REPORT DOCUMENTATION PAGE	*Form Approved* *OMB No. 0704-0188*

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	18 Apr 97	

4. TITLE AND SUBTITLE
VENOCONSTRICTIVE CUFFS IMPEDE FLUID SHIFTS DURING SIMULATED MICROGRAVITY

5. FUNDING NUMBERS

6. AUTHOR(S)
KJELL N. LINDGREN

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
COLORADO STATE UNIVERSITY

8. PERFORMING ORGANIZATION REPORT NUMBER
97-022

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
DEPARTMENT OF THE AIR FORCE
AFIT/CI
2950 P STREET
WRIGHT-PATTERSON AFB OH 45433-7765

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION AVAILABILITY STATEMENT

DISTRIBUTION STATEMENT A
Approved for public release;
Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

19970428 173

14. SUBJECT TERMS

15. NUMBER OF PAGES
97

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT

DTIC QUALITY INSPECTED 1

Standard Form 298 (Rev. 2-89) (EG)
Prescribed by ANSI Std. 239.18
Designed using Perform Pro, WHS/DIOR, Oct 94

THESIS

VENOCONSTRICTIVE THIGH CUFFS IMPEDE FLUID SHIFTS DURING SIMULATED MICROGRAVITY

Submitted by

Kjell N. Lindgren

Department of Physiology

In partial fulfillment of the requirements

for the Degree of Master of Science

Colorado State University

Fort Collins, Colorado

Fall 1996

Copyright© by Kjell Norwood Lindgren 1996
All Rights Reserved

COLORADO STATE UNIVERSITY

November 13, 1996

WE HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER OUR SUPERVISION BY KJELL N. LINDGREN ENTITLED <u>VENOCONSTRICTIVE THIGH CUFFS IMPEDE FLUID SHIFTS DURING SIMULATED MICROGRAVITY</u> BE ACCEPTED AS FULFILLING IN PART REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE.

<u>Committee on Graduate Work</u>

[illegible]

Robert Gotshall

Alan Tucker
Adviser

Alan Tucker
Department Head

ABSTRACT OF THESIS

VENOCONSTRICTIVE CUFFS IMPEDE FLUID SHIFTS DURING SIMULATED MICROGRAVITY

Long duration exposure to the microgravity environment has detrimental effects on the human body. Primary to the changes seen in the cardiovascular system are microgravity-induced fluid redistributions, the adaptation to which result in orthostatic intolerance when re-exposed to normal gravity. Venoconstrictive cuffs could be used to impede the fluid shifts and consequently change the overall distribution. Ten healthy male subjects were exposed to a 2.5-hour tilt protocol which started in the standing position, and was followed by 30 min supine, 30 min standing, 30 min supine, 30 min of -12° head down tilt (HDT; to simulate microgravity), 15 min of HDT with venoconstrictive thigh cuffs inflated, 10 more min of HDT, 5 min supine and 10 min standing. Transition to the various tilt postures resulted in concomitant changes in leg volume (Stand [STD] to Supine [SUP] -3.0%, SUP to HDT -2.0%). Inflation of the venoconstrictive thigh cuffs to 50 mmHg during simulated microgravity resulted in a 3.0% increase in leg volume from that seen in HDT. This increased leg volume

represents a favorable fluid redistribution throughout the body. No changes in systemic cardiovascular parameters were noted during cuff inflation.

Leg volumes were measured with anthropometric and strain-gauge plethysmography. The more definitive anthropometric measurements were used to assess strain gauge plethysmography as a valid index of leg volume changes using regression ($r=0.86$, $p<0.01$) and paired t-test ($p<0.05$) analysis. Cuffs could potentially be used to ameliorate the symptoms of congestion seen with Space Adaptation Syndrome and to potentiate existing volutropic countermeasure protocols.

Kjell N. Lindgren
Department of Physiology
Colorado State University
Fort Collins, CO 80523
Fall, 1996

ACKNOWLEDGEMENTS

I offer a sincere thanks to the following individuals, for making my graduate program such a terrific experience.

-First and foremost, I thank God for the tremendous opportunities that he has given me. I could not have asked to work with a more outstanding group of people, in better locations and on a more ideal project, than I have in the past year and a half.

-To my advisor, Dr. Alan Tucker, for accepting me into this program, and for patiently guiding me through the Masters process.

-To my committee members, Drs. Robert Gotshall and Robert Phillips, for their guidance and support during the thesis process.

-To Dr. Alan Hargens at NASA-Ames, for letting me work in his lab. Conducting research in association with NASA was a dream come true for me. The summer experience, both in the lab and roaming the Bay area, is one I will never forget.

-To Rick Ballard, manager of the Space Physiology Lab at NASA-Ames, for facilitating this research. Without Rick's help this project would never have been accomplished.

-To Karen Hutchinson and everyone else at NASA-Ames that assisted in the completion of this research.

-To Dr. Daniel Kraft, for conceiving this project and allowing me to conduct it in his absence.

-To Dan Page, Ruth Howard and Johnna Gaswint in the CSU Physiology office, for their invaluable help and patience during the course of my academic program.

-To my friends, colleagues and professors at CSU for making the past year and a half so enjoyable and educational.

-To the U.S. Air Force and Air Force Academy Biology Department for providing me with the opportunity to pursue a Masters degree.

-To my AFIT colleagues, Major Holly Franz, Major Edward Unangst, Lieutenant Colonel Craig Seabaugh, and Lieutenant Tara Nolan for their advice and guidance.

-To my fellow space physiologist, NASA scientist and friend, Tony Artino, for his generosity, humor, advice and assistance, and for pushing me to do my best. I wish him the best of luck in the Navy and beyond.

-To my parents, Randahl and Anita, and my sister, Niki, for their constant love and support.

-To my girlfriend, Kristiana Jones, for her patience, love and encouragement.

TABLE OF CONTENTS

"the question is not really whether we, either as a nation or a planet, will make the Journey. The question is when."

S.F. SHEA
Chairman of the Space Systems and
Technology Advisory Committee

This manuscript is dedicated to the memory of C2C David Wayd Weber.

LIST OF TABLES

LIST OF FIGURES

CHAPTER I

INTRODUCTION

Ignited by the genius of Tsiolkovsky, Goddard and Oberth, fueled by the hypergolic elements of the Cold War, restrained by the drag and friction of tragedy and budget restraints, and boosted by recent discoveries of possible life on Mars, the human exploration of space remains one of mankind's greatest accomplishments and as well as one of its greatest future challenges.

The human payload remains the most fragile (and valuable) element in any manned mission. The preservation of that element is of the utmost priority, and as missions become longer in duration, meeting that priority becomes more challenging. A manned mission to Mars may take in excess of two years (84). Future hopes of colonization will require even longer stays in a reduced gravity environment. Exposures of this duration can have devastating effects on the human body if not checked by viable countermeasures. No mission can be successful if the astronauts are unable to return to the strain of earth's gravity.

The microgravity environment associated with spaceflight has a number of significant effects on the human body, one of which is a net shift of fluid into the thoracocephalic compartment. This fluid shift has a number of immediate and long term implications. Initially, this cephalad fluid distribution causes signs of facial edema, eye

redness and "bird" legs and symptoms of congestion, stuffiness and headaches. This headward fluid shift may also contribute to space motion sickness (4,65). Long term cardiovascular implications include a net decrease in fluid volume, baroreflex attenuation, a decrease in circulating red cell mass and possible increases in leg venous compliance. A decreased overall fluid volume coupled with a diminished baroreceptor reflex and increased venous pooling can cause orthostatic intolerance during re-exposure to normal gravity. The possibility of syncopal episodes during re-entry and potential post-flight emergencies are of operational concern. Therefore, the development of countermeasures to combat cardiovascular deconditioning and orthostatic hypotension is necessary.

Lower body negative pressure (LBNP), exercise, medication, axial compression suits and fluid loading have all been used in flight to minimize muscle atrophy, bone demineralization, and cardiovascular deconditioning (17,32,77). Other possible countermeasures have been evaluated, but discarded for lack of positive results, while future countermeasures remain to be tested. The uses of venoconstrictive thigh cuffs have not been adequately investigated. While prevalent in compliance and flow studies, their possible applications in a microgravity environment have not been sufficiently explored. Research in the 1960's on venous occlusion cuff use in microgravity generated various conflicting data and resulted in little further research (78). Cosmonauts have used occlusive thigh cuffs, the "Bracelet", in flight with beneficial reduction of congestion and facial edema (3,56).

The use of venoconstrictive thigh cuffs essentially occludes venous flow from the legs until the trapped upstream venous volume generates pressures greater than that caused by the cuff. While flow resumes as normal, a greater distribution of blood and

higher venous pressures may exist in the limb segments distal to the cuff. While this volume trapping may not have any significant cardiovascular effects (e.g. on heart rate or blood pressure), it could be used to create a more earth-like fluid distribution in the body. This distribution could be potentially useful in 1) ameliorating the symptoms of congestion and headache upon initial exposure to microgravity and 2) in potentiating other existing countermeasure protocols prior to re-entry.

Hypothesis and Specific Aims. The purpose of this study was to investigate the effects of venoconstrictive cuffs on the body's fluid distribution during simulated microgravity. This study was designed to test the following *hypothesis*: venoconstrictive thigh cuffs, inflated to 50 mmHg during simulated microgravity (as modeled by -12° head down tilt [HDT]), will impede venous flow resulting in increased leg blood volumes and thereby changing the whole body fluid distribution to one more similar to that seen while standing in a normal-g environment. This hypothesis will be evaluated by addressing the following *specific aims:*

1. Measure leg volume changes, using strain gauge, impedance and anthropometric sleeve plethysmography, to determine the efficacy of venoconstrictive thigh cuffs.
2. Describe the time course of leg volume changes during various tilt exposures and venoconstrictive cuff inflation.
3. Make a quantitative comparison of the plethysmography techniques.
4. Evaluate the systemic cardiovascular responses by tracking heart rate and blood pressures.

CHAPTER II

REVIEW OF LITERATURE

Every human grows and develops under the strain of gravity. Organ systems, organs, tissues and cells have all adapted to this pervasive force, utilizing it, combating it, adjusting to it as a part of daily life. The absence of gravity then, demands subsequent physiological response. Spaceflight and the inherent exposure to the microgravity environment has numerous physiological effects on the human body.

The absence of gravity affects systems throughout the body ranging from the neurovestibular apparatus to the cardiovascular system, from hormones and metabolism to the very makeup of bones and muscles (61). The absence of a gravity vector causes a variety of problems in perception and sensory function, leading to decreased proprioceptive and postural awareness and debilitating Space Motion Sickness. The muscles and bones which are usually constantly straining against the force of gravity, fall into disuse and begin to atrophy. Some of the more noticeable changes, those that are intimately related to this study, occur in the cardiovascular system.

Microgravity and the Cardiovascular System

In very general terms, the role of the cardiovascular system is to provide oxygen and nutrients to the body and to remove CO_2, metabolites and other waste products. Of

the organs it supplies, none is more critical than the brain. With no storage capacity for high-energy phosphate compounds, the brain cannot survive diminished perfusion and oxygenation for even a short period of time (71). Within seconds the tissue becomes ischemic and if blood flow is not restored, cellular dysfunction and unconsciousness follow (68).

When moving from a supine to a standing position, a complex series of processes occur in the healthy body to maintain perfusion of the brain, to adjust to the hydrostatic challenge on the cardiovascular system. The hydrostatic component of vascular pressures is evident in the fact that cerebral arterial pressures are maintained at approximately 70 mmHg while arterial pressures at the feet can reach 200 mmHg (35).

Movement to the upright position causes a shift of 300-400 ml of fluid from the central compartment to the legs (24,60). This postural decrease in central volume is followed by decreases in stroke volume and cardiac output (68). These volume changes are detected by the centrally located aortic and carotid baroreceptors which initiate increased sympathetic outflow and vagal withdrawal (23). Elevated sympathetic tone results in constriction of arteriolar precapillary sphincters, which increases total peripheral resistance (TPR), and venoconstriction of the peripheral venous network, which mobilizes the venous blood reserve (23). In addition, vagal withdrawal and increased sympathetic tone cause an increase in heart rate, which, combined with increased TPR, result in a maintenance of arterial blood pressure sufficient to perfuse the brain and the rest of the body. The relationship between these hemodynamic variables is illustrated by the following equations:

$$CO = HR \times SV \qquad \textit{(Equation 1)}$$

$$MAP = TPR \times CO \qquad \textit{(Equation 2)}$$

where CO = Cardiac output
HR = Heart rate
SV = Stroke volume
MAP = Mean arterial pressure
TPR = Total peripheral resistance

By substituting the equation for cardiac output into the equation for mean arterial pressure, it is easy to see the transient changes that occur to maintain arterial blood pressure.

$$\uparrow TPR \times \uparrow HR \times \downarrow SV = \leftrightarrow MAP \qquad \textit{(Equation 3)}$$

In certain disease states the cardiovascular system does not adequately respond to the orthostatic challenge (68). If postural decreases in volume are not met with compensatory changes in HR and TPR, mean arterial pressure falls, followed by a subsequent decrease in arterial pressures at the head. Cerebral pressures below 60 mmHg generally result in presyncopal symptoms of dizziness, nausea and lightheadedness (68). If pressures remain depressed, syncope will result. The inability to sustain upright posture is called orthostatic intolerance. This postural hypotension is also seen in astronauts returning from microgravity due to pathophysiological processes that will be discussed later in this review.

General Physiology of Microgravity. A translocation of fluid from the lower body into the thoracocephalic compartment upon exposure to the microgravity environment is primary to the changes seen in the cardiovascular system. The signs and symptoms associated with these physiological changes were among the first documented in manned

spaceflight (60). Anecdotal reports of facial edema, congestion, distended face and neck veins and “bird legs” provide visible indication that fluid distributions have been modified to some degree (60,71,73). This headward shift of fluid occurs as a result of the absence of a gravitationally-induced hydrostatic gradient, but the associated physiological changes may occur even before liftoff, as the astronauts spend at least two hours in a recumbent “pre-launch” position, with their legs elevated above their hearts (27,35). Indeed, Gotshall et al. (27) found that some measure of cardiovascular deconditioning occurs after 2 hours in this HDT position.

Models of Microgravity. Physiological flight data are limited. The relatively few number of subjects, combined with busy schedules and inconsistent conditions, have caused investigators to develop ground-based methods of mimicking the physiological responses to microgravity (23). Numerous models have evolved over the years in an effort to not only study the changes caused by spaceflight, but also to develop and test countermeasures to those changes. Of these models, water immersion, supine bed rest and head-down tilt (HDT) have been used most frequently (34,74). The supine position eliminates a long axis hydrostatic gradient, while head-down tilt actually induces a slight $-G_z$ headward hydrostatic column that mimics the cephalad fluid shift seen in microgravity. In 1987, Tipton et al. (75) recommended -5° HDT for simulating the general effects of microgravity. Nixon et al. (62) established the validity of the -5° HDT model by comparing fluid distributions, and post-flight exercise and orthostatic tolerance to Apollo and Skylab results. Conversely, Tipton et al. (74) observed that the water immersion model is “not the most desirable because the Henry-Gauer reflex has not been

effectively demonstrated in space, the compression of soft tissue and the large pressure gradient across the chest wall are not features of microgravity." While all of these models mimic many of the physiological changes seen in microgravity, they are not perfect (35). Gravity still exerts a force on the body, and the weight of abdominal contents and muscles can cause transmural pressures not seen in space (35). As a result, the collection of flight data remains the most important tool in determining physiological responses to a true microgravity environment.

Significance of Leg Volumes. Since fluid shifts are one of the primary and preeminent changes seen in microgravity, some measure of the degree of shifting is essential. Decreases in leg volume were qualitatively noticed early in the space program, as evidenced by reports of 'bird legs.' Since the physiological implications of this "shifted" volume are important, especially with early concerns that cardiac performance might be compromised by a volume/pressure overload, a method of measuring leg volumes was developed. Because a large percentage of the fluid volume shifted in microgravity comes from the dependent limbs, changes in leg volume can provide some quantitative measure of fluid translocation. Made on an accessible part of the body, leg volume measurements are non-invasive, easily performed and consequently serve as an index of fluid shift both during ground simulations and in-flight.

Volume measurement methods. Strain-gauge, impedance and fluid plethysmography and serial circumferential measurements are all accepted methods for leg volume estimation. Fluid plethysmography estimates leg volumes via fluid displacement. While it is probably the most definitive method of volume measurement, it is laborious and its

use is confined to ground studies. Many researchers utilize fluid plethysmography as a standard for validating other measurement methods (70).

Whitney strain gauge plethysmography bases its volume estimation on the circumferential changes seen in one plane of the maximal calf girth (86). In most cases a dual strand mercury-in-silastic strain gauge is placed around the calf at its maximal girth. As the calf circumference changes, the silastic tube changes in length and width. These changes in tube dimension cause concurrent voltage and resistance changes across the resident mercury column, which can be calculated out as percent change in leg circumference (86).

The impedance plethysmograph estimates fluid volume shifts according to the measured resistivity of each defined body segment (52,58,59). A small current is introduced into a distal lead, and various electrodes along the body measure the resistance or impedance to that current (52,58). Water is essentially the most conductive material in the body. As water content in a certain segment of the body decreases, the measured impedance in that segment will increase, and vice versa (58).

It is also possible to measure the volume of the leg using serial circumferential measurements (43,60,70). These measurements generate a number of circular cross-sectional areas that can be used to estimate a series of truncated conical volumes that represent total leg volume (43,60,70). This plethysmographic method, like the those mentioned before, is based on certain assumptions that must be accounted for in the final data analysis.

Leg Volume Losses. Measurements obtained during five Shuttle missions indicate a loss of about 1 liter from each leg, representing an 11.6% decrease in leg volume (60).

Skylab and Apollo-Soyuz Test Project data are similar with 931 ml (12.2%) and 803 ml (10%0) leg volume deficits, respectively (42,60,71). Moore et al. (63) demonstrated that a greater percentage of the leg fluid shift came from the mid-thigh (69%) than from the calf (31%). The thigh lost 12% of its volume while the calf only lost 9.4% (60). This relative-loss distribution is different from that seen in HDT and bed rest studies, where relatively more volume is lost from the calf (70).

The leg volume changes occur in two phases, an initial rapid decrease and a slower component that occurs over the course of the mission (48,60). The abrupt nature of the initial volume decrease can only be due a translocation of fluids, while the slower component is probably due to extravascular fluid loss and muscle atrophy (36,60,72). The rapid leg volume reduction and consequent facial edema and congestion is indicative of the cephalad movement of fluid. The slower transcapillary component of leg volume reduction is governed by Starling forces (34). Transition to microgravity, and the elimination of hydrostatic pressures, results in the predicted reduction of leg venous pressures from ~90 to ~30 mmHg (34,46). The resultant decrease in capillary pressures elicits a shift from filtration to net reabsorption (51,73). Using the wick-catheter technique, Hargens (36) demonstrated decreased interstitial fluid pressures in the tibialis anterior muscle and surrounding subcutaneous tissue after 4 hours of -5° HDT. And trends towards decreased water content in the soleus muscle suggests a net fluid shift from the lower limb tissue to the vascular space (33,36). Based on HDT measurements, Hargens (36) indicates that "interstitial fluid is lost at $12 ml \cdot h^{-1}$ from tissues that comprise about 65% of lower-leg volume."

Nature of the Fluid Shift. Removal of the hydrostatic column essentially causes fluid to shift according to the vascular compliance of tissues throughout the body (71). In upright posture (normal g), the dependent venous vasculature is subjected to the distending pressures of the hydrostatic column (approx. 90 mmHg) (34). The deep veins of the legs are engorged with blood and the venous tissue operates on a relatively flat portion of the compliance curve. Meanwhile, the upper venous network is exposed to lesser pressures and as a result operates on a steeper portion of the compliance curve. Removal of the hydrostatic component results in an equalization of venous pressures throughout the body to about 30 mmHg (34). As the pressures equalize, volume moves from the relatively non-compliant lower limbs to the available space in the more compliant upper vasculature (71). Poor volume/flow regulating characteristics of the upper body allow the "abnormal" volume distribution to remain (34).

Leg Blood Flow in Simulated and Actual Microgravity. Panferova et al. (63) measured blood flow velocity in the lower limbs during upright, supine, -12° and -22° HDT. They interpret their data to suggest a decrease in volumetric blood flow rate in the legs, with a relatively smaller decrease in blood efflux than influx and that the higher outflow is responsible for the overall decrease in leg volume (63). They suggest that the "dramatic slowing of peripheral blood flow and, consequently, diminished influx of blood to the limbs…is attributable to central mechanisms of regulation and depended little on local changes in hydrostatic pressure of fluid in the extremities." Panferova et al. (63) indicate that this limitation of influx is important in protecting the central volume and heart from being overloaded. While relative differences in leg inflow and outflow

certainly contribute to the shift of fluid to the central compartment, no available data corroborate any centrally-mediated cardioprotective increase in arteriolar tone. On the contrary, flow to the skeletal muscle of the leg is largely regulated by local control mechanisms (5).

Skylab data suggest that blood flow to the legs is actually increased in microgravity (72). Thornton et al. (72) propose that the increase in leg blood flow may be secondary to the increased cardiac output observed in microgravity. These increased blood flow measurements do not contradict data indicating decreased leg volumes. In the absence of the distending pressures of the hydrostatic column, the deep capacitance veins of the legs remain relatively empty and may serve more as a conduit than a storage vessel.

Hemodynamic Changes. The cephalad fluid shift has widespread effects on the cardiovascular system. Measurements taken during the first few mission days reveal decreases in heart rate, diastolic blood pressure, central venous pressure (CVP), plasma volume, total blood volume, red blood cell mass and total peripheral resistance (1,7,23,46,67,69,76,89). Stroke volume, cardiac output and left ventricular end diastolic dimensions are increased (7,66,69,89). These changes are all ostensibly initially related to the increased central blood volume.

Of these changes, the in-flight decrease in CVP was a surprise to many researchers (7). It was first hypothesized that the fluid shift-induced increase in central blood volume would cause a subsequent increase in CVP (72). Catheterization data from three subjects clearly show a decrease in CVP which Buckey et al. (7) suggest may be

due to a combination of relaxation of the venous smooth muscle and a decrease in blood volume.

Fluid Volume Changes. Decreases in blood and plasma volume have been noted since the Gemini program (39). Data from shuttle missions SLS-1 and SLS-2 indicate a 17% decrease in plasma volume after only 22 hours in space (1,17). Data from SLS-2 also noted a 12% decrease in total blood volume at landing (76). Despite the dramatic change in plasma volume, peripheral venous hematocrit did not change significantly. Alfrey et al. (1) suggested that this may be due to the change in red blood cell size, allowing more cells to be packed into a similar volume. However, estimated total body hematocrit did increase by flight day 2 (76). A hemoconcentration-derived increase in hematocrit would be expected due to rapid volume depletion without a commensurate decrease in red blood cell mass (50). Hinghofer-Szalkay et al. (37) described similar changes in plasma and blood density with head down and head up tilt. Essentially, the greater the angle of tilt in either direction from supine, the denser the blood becomes (37). Prior to landing, plasma volumes never return to pre-flight levels, suggesting that a new homeostatic level, or set point, is established (50).

A number of processes contribute to these decreases in fluid volume. First of all, centrally located volume receptors cannot differentiate between the exaggerated central blood volume and an increase in total blood volume, and consequently initiate a neurohumeral cascade to elicit a volume reduction via diuresis (13). However, no initial diuresis has been documented in spaceflight (38,50). Astronauts have reported that the recumbent, legs-elevated prelaunch position produces a diuresis, but these urinary excretion volumes have not been recorded (7,34,38,60). To confound the data even

further, many astronauts limit fluid intake prior to flight in an attempt to avoid the need to urinate while waiting to launch (7). This decreased fluid intake, coupled with a possible increase in insensible water loss, could contribute to a decreased plasma volume even before exposure to microgravity (7).

Further decreases in plasma volume can be attributed to transcapillary fluid shifts from the vascular compartment to the extravascular compartment in the upper body. Studies conducted by Parazynski et al. (64) and Hargens et al. (34) suggest that the capillaries in the upper body are thinner and have poor regulating characteristics as compared to the capillaries found in the feet. If so, the higher cephalad pressure generated by the fluid shift could promote the shift of protein rich fluid from the vascular space (50). Leach et al. (50) propose that decreases in plasma and extracellular fluid volume in view of unchanged total body water indicate an increase in intracellular fluid volume.

The physiological changes seen in microgravity are appropriate to the environment, and have a benign effect on the cardiovascular system (23,34). These changes, however, are maladaptive in a normal gravity context, and can have deleterious effects on cardiovascular performance upon return to Earth.

Postflight changes. The various cardiovascular adaptations to microgravity that make an astronaut more susceptible to orthostatic hypotension when re-exposed to normal gravity are collectively known as 'cardiovascular deconditioning.' Researchers generally attribute the incidence of orthostatic intolerance to three main components: decreased blood volume (40,50,76), excessive peripheral venous pooling (9,16,72) and an attenuation of the arterial baroreflex (20,21,22,32).

Microgravity induced hypovolemia. First of all, the microgravity-induced decreases in plasma and total blood volumes result in hypovolemia on Earth. Data from SLS-1 indicate that plasma volume was still decreased 11% below preflight values, while data from STS-40 show total blood volume at landing was decreased 12% (50,76).

Introduction of a hydrostatic gradient upon return to a normal-g environment forces a percentage of the reduced total volume into the dependent vasculature, so that volumes adequate for perfusion in microgravity are insufficient in normal-g. In essence this reverse fluid shift causes a hypovolemic state which can result in decreased central blood volume, stroke volume, cardiac output and arterial pressure. Inadequate perfusion pressures at the brain then result in presyncopal symptoms of nausea, dizziness and lightheadedness, i.e. orthostatic intolerance.

Venous pooling. A second possible component of cardiovascular deconditioning could be due to excessive peripheral pooling in a more compliant dependent venous vasculature. The deep veins of the leg are responsible for ~85% of venous volume (10). Many investigators (10,72) suggest that these veins have little intrinsic structure of their own, and rely mainly on the surrounding musculature for compliance and capacitance characteristics. Buckey et al. (10) determined that these 'passive' deep veins are responsible for 90% of volume changes at low levels of occlusion (40 mmHg) and 51% of the volume increases at higher occlusive pressures (100 mmHg). These capacitance vessels rely on the surrounding muscle and connective tissue for structural support, muscle tissue that loses tone and mass due to disuse atrophy both in simulated and actual spaceflight (72). In fact, Convertino et al. (14,15,16) demonstrated that calf muscle cross sectional area was significantly correlated with percent change in calf compliance. While

it has been shown that high leg compliance is related to low orthostatic tolerance, there is controversy as to whether simulated or actual microgravity really has any significant effect on leg compliance (15,54,55,57,72). Still, even if the dependent veins are not more compliant, and yet allow the same absolute volumes to pool in the legs, this fraction of blood represents a larger percentage of the microgravity-reduced total blood volume and orthostatic intolerance may result (8,9).

Baroreflex attenuation. A third component of orthostatic intolerance involves a diminished arterial baroreflex response. Arterial blood pressure is challenged by postural volume changes many times a day in normal humans (23). Chronic lack of orthostatic challenge in microgravity may result in a blunting of baroreceptor sensitivity (23,35). Supine heart rate, systolic and diastolic blood pressures, plasma catecholamine levels, and peripheral vascular resistance are all elevated postflight, consistent with overall sympathoexcitation and vagal withdrawal (23). However, Buckey et al. (8) saw inadequate heart rate and total peripheral resistance responses in astronauts who became orthostatic during a post-flight operational stand test.. Fritsch-Yelle et al. (20,21,22,23) described that while "heart rate increases are exaggerated from preflight values, stroke volume, cardiac output, and peripheral vascular resistance are not, and arterial pressure is not well maintained." Whitson et al. (88) suggested a decrease in end organ responsiveness, as increased levels of norepinephrine during post-flight standing failed to elicit proportional changes in TPR. Buckey et al. (8) point out, however, that plasma levels of hormone messenger do not reflect availability at the receptor level. All of these inappropriate responses suggest some deficit in the arterial baroreflex arc.

Countermeasures

In astronauts returning from the SLS-1 and SLS-2 missions, 64% were unable to complete an operational stand test (29 minutes supine followed by 10 minutes standing) (8). Fritsch-Yelle et al. (22) reported that 25% of astronauts that flew from 8-14 days had presyncopal symptoms during stand tests or during shuttle egress. This incidence of orthostatic intolerance is of operation concern.

Unlike previous "capsule" spacecraft, the space shuttle returns to the Earth in a glider configuration, exposing its crew to up to 1.5 $+G_z$ during re-entry (61). Cardiovascular deconditioning may impair an astronauts ability to respond to emergency situations in the presence of gravitational stress. Likewise, in future long duration missions of planetary exploration or colonization, astronauts must be able to withstand gravitational stress and operational workloads. Compromised cardiovascular function, if not addressed, will diminish the astronauts ability to perform and very possibly endanger their lives.

In order to maintain the cardiovascular system and decrease the incidence of postflight orthostatic intolerance, investigators have devised various countermeasures to either slow the rate of deconditioning, or to prepare the individual for normal gravity prior to re-entry. Some of the more productive countermeasures include fluid loading, Lower Body Negative Pressure (LBNP), exercise, g-suits and medication.

Fluid loading. The fluid loading protocol specifically addresses the microgravity-induced hypovolemia. Initial bedrest studies demonstrated that ingestion of isotonic saline solutions (in the form of bouillon) increased subject tolerance to LBNP and acceleratory stress, ostensibly by supporting the vascular volume (29,32,41). It was

subsequently adopted for use on the shuttle, and became the first countermeasure addressing microgravity-induced changes, to be applied acutely and meet with success (11,32). The operational protocol involves ingesting a 1 gram salt tablet for every 4 ounces of water up to a total one liter of approximately isotonic saline (11,32). All of the crewmembers who used the countermeasure completed the post-flight stand test, while 33% of those who did not use the countermeasure became presyncopal/syncopal (11,13). Additionally, those astronauts who underwent fluid loading had lower standing heart rates and regulated arterial blood pressure better than their non-CM associates (11,13). While fluid loading proved to be beneficial, its effectiveness may be limited to missions of under a week duration (17). Fluid loading failed to raise plasma volume after 7 days of HDT and had no significant effect on orthostatic heart rate after 7 days of flight (17,77,87).

LBNP. Lower body negative pressure (LBNP) was utilized to provide orthostatic challenge to the cardiovascular system in microgravity. In this system, a rigid container encompasses the lower body up to the iliac crest. A rubber skirt establishes a seal, below which a negative pressure is introduced. The 'vacuum' essentially pulls fluid into the lower body, inducing an orthostatic-like challenge on the cardiovascular system, forcing it to regulate arterial blood pressure. Operationally, the Skylab astronauts were exposed to a 25-minute protocol with -10 mmHg steps down to a maximum vacuum of -50 mmHg (42). Investigators reported its success in decreasing cardiovascular deconditioning during spaceflight and bedrest (25,30,31).

LBNP was also conducted in conjunction with the fluid loading or 'soak' protocol. Crewmembers were subjected to 4 hours of LBNP at -30 mmHg with a

standard fluid load of 1 liter isotonic saline given at the beginning of the protocol (67). This resulted in increased orthostatic tolerance, as evidenced by decreased heart rate responses to LBNP and increased plasma volumes for the subsequent 24 hours (13). LBNP has been removed from operational use, however, as its benefits were outweighed by time constraints, crew discomfort, and its awkward operation (Shao, personal communication).

Other countermeasures include the use of exercise to decrease muscle and skeletal atrophy, and modified g-suits to increase peripheral resistance and support blood pressure. These and other countermeasures have met with measured success.

Venoconstrictive cuffs. Venous occlusion cuffs, essentially constrictive cuffs placed around the thighs to occlude venous flow, were investigated as a possible countermeasure in the late 1960's (6,12,28,56,78,79,80,81,82). While venoconstrictive cuffs find widespread use in compliance and flow studies, they have no role in the current countermeasure regimen (32,67,72).

Research conducted in the late 1940's demonstrated that whole body oscillations diminished the cardiovascular deconditioning seen with bedrest (86). Graveline (28) suggested that the results of this intervention, which introduced intermittent hydrostatic components to the vasculature with concomitant decreases in venous return, could be mimicked with the intermittent inflation of peripheral occlusive tourniquets. The results of his immersion study, which utilized venoconstrictive arm and leg cuffs, inflated to 60 mmHg in a one minute on/off cycle, seemed to verify his hypothesis. Subjects exposed to this countermeasure regimen demonstrated relatively greater orthostatic tolerance in post-exposure tilt tests than the non-cuffed controls. Vogt et al. (42) confirmed these

results in a similar immersion study. Further research, however, yielded contrary results. Several subsequent bedrest studies conducted by Vogt et al. (79,81,82,83) indicated that combinations of leg cuffs, leg and arm cuffs, with various timing cycles afforded no protection from cardiovascular deconditioning as established by tilt table tests. The further evaluation of leg cuffs in spaceflight during Gemini V and Gemini VII yielded no cardiovascular protection, leading Vogt et al. (83) to conclude that 1) there were no use for cuffs, 2) that further evaluation of cuff configuration or timing cycles was not warranted, and 3) that other means should be used to prevent cardiovascular deconditioning. The protocols and results obtained in these studies suggest that the researchers were strictly looking for hemodynamic changes and improved post-flight orthostatic tolerance.

Little descriptive or quantitative research has been conducted since. The most recent research was published by Katkov et al. (47) in 1981 and by Gazenko et al. (26) in 1982. Katkov et al. (47) demonstrated that venocclusive cuffs, inflated to 40 and 60 mmHg caused an increase in dorsum pedis venous pressure, a decrease in oxygenated hemoglobin and an increase in the arteriovenous O_2 difference. Gazenko et al. (26) described similar increases in venous pressure with no changes in arterial pressure during application of mechanical and pneumatic lower extremity cuffs. They further quantified the changes seen in central venous pressure (CVP) and pulmonary artery pressure (PAP) among other variables. Mechanical extremity cuffs, applied to the upper thighs at 40 and 60 torr (as measured by tissue pressure) during -20° HDT caused significant changes from HDT baseline, that were similar (not significantly different) to hemodynamic

variables seen during orthostasis (26). Pneumatic cuffs applied at the same pressures did not have the same effect. While there were some hemodynamic changes, the values remained significantly different from those seen during head up tilt. The authors contribute the differences seen between mechanical and pneumatic cuffs to measurement methods. The mechanical cuffs were measured with tissue pressures while pneumatic cuffs were applied according to cuff pressures. They quantified the benefits of these cuffs according to their ability to reduce CVP and PAP. But these variables have subsequently been shown not to be elevated in microgravity (7). While Katkov et al. (47) and Gazenko et al. (26) both assumed dependent venous volumes were increased with venous occlusion, these changes were not measured.

Venoconstrictive thigh cuffs were utilized by cosmonauts, reportedly improving "the health state of Soyuz-38 crewmembers who showed motion sickness" (56). However, no quantitative analysis was performed, and cuff use was discontinued.

Nothing in the available literature quantifies the effect venoconstrictive cuffs may have on microgravity-induced fluid distributions and the resultant symptoms of congestion, facial edema or even SMS. Similarly, the literature does not establish what effects venoconstrictive cuffs may have in conjunction with established countermeasures, such as LBNP, fluid loading or pharmacological interventions. The purpose of this study, then, was to quantify leg volume changes seen with the inflation of venoconstrictive cuffs to 50 mmHg during simulated microgravity (-12° HDT).

CHAPTER III

MATERIALS AND METHODS

Subjects. Ten healthy male subjects (age 28 ± 3.1 yrs, height 177.2 ± 1.6 cm, weight 75 ± 2.8 kg, mean ± S.E.) volunteered to participate in this study, which was approved by the NASA Ames Human Research Institutional Review Board and the Colorado State University Human Research Committee. The details and risks associated with the study were explained to each subject before written consent was obtained. The subjects were healthy, normotensive nonsmokers with no history or symptoms of cardiovascular or peripheral vascular disease.

Instrumentation. Blood pressure was monitored using two different methods. Continuous measurements were made using the Peñaz technique with a Finapres® finger cuff (Ohmeda, Englewood, CO), while left arm Korotkoff sounds were auscultated and recorded every five minutes. Heart rate was continuously monitored by the Finapres®, and recorded every five minutes as the interval measurement. ECG was not used because of concerns that the leads would have caused multiple grounding conflict with the impedance plethysmography equipment.

Leg volume changes were measured using three different systems: impedance plethysmography; 'volume sleeve' anthropometric plethysmography; and strain gauge plethysmography:

1) Impedance measurements, based on the impedance or resistivity of identified body segments, were made using a specialized computer-controlled Tetra-polar High Resolution Impedance Monitor (THRIM) (UFI, Inc., Morro Bay, CA). After site exposure, hair removal and alcohol prep, nine disposable ECG electrodes (3M, St. Paul, MN) were placed along the length of the subjects' right side, at the hand, wrist, elbow, shoulder, iliac crest, upper thigh, knee, ankle and foot. Excluding the hand and foot 'excitation' leads, these electrodes essentially divided the body into 6 defined segments. The THRIM introduced a high frequency (~50 kHz), low amperage (0.1 mA rms) constant electrical current between the hand and foot electrodes (59). The seven monitor electrodes recorded simultaneous baseline resistances (R_0) for each segment at a sampling rate of .25 Hz.

Impedance plethysmography is based on serial segmental impedance measurements. The introduction of an electrical current causes the body to act as a volume conductor, with continuous lines of electricity distributed in three dimensional paths (58). Changes in fluid volume and tissue characteristics have measurable effects on this flow of electricity (52). Blood is the most conductive tissue in the body, so as the volume of blood in a specified segment increases, the resistance, or impedance to electrical flow is reduced (52). By making serial impedance measurements of a given segment, a change in volume over time can be established.

Generally, resistance in a given conductor is directly related to length and resistivity factor (resistivity of $1 cm^3$ of the subject material) and inversely related to cross-sectional area (58) or:

$$R = \frac{\rho L}{A} \qquad \textit{(Equation 4)}$$

where R = resistance (ohms)
ρ = electrical resistivity of the subject material/tissue (ohm-cm)
L = length of the conductor or segment (cm)
A = cross-sectional area of the conductor/segment (cm^2)

Since volume (V) $=AL$, multiplying Equation 4 by L/L results in:

$$R = \frac{\rho L^2}{V} \qquad \textit{(Equation5)}$$

Solving for volume, Equation 5 can be written:

$$V = \frac{\rho L^2}{R} \qquad \textit{(Equation 6)}$$

Having measured the distance *(L)* between adjacent segment electrodes and resistance with the plethysmograph, and by assuming a tissue resistivity factor of ~150 ohm-cm, segment volumes, and subsequently, volume changes can be calculated (58).

Unfortunately, during the course of the experimental protocol, the impedance-computer interface experienced a number of framing errors and error loops. While a triple plethysmograph comparison would have been interesting, the impedance data were rendered unusable and will not be reported.

2) Anthropometric measurements were made using a 'sleeve' of 9 circumferential non-distensible tape measures (6 below the knee, 3 above), in a system similar to that described by Thornton et al. (70). This measurement method, developed by Jones et al. (43), and validated by Thornton et al. (70) against a fluid plethysmograph (r=.995) is based on a series of circumferential girth measurements along the leg. The leg is divided into a number of segments, marked by proximal and distal measuring tapes. The

resulting circumferential measurements can be used to calculate the area of a truncated cone, that when summed with the other segment areas, provides an accurate total leg volume (Figure 1 and Equations 7-9) (70).

$$R, r = \frac{circumference}{2\pi} \qquad \text{(Equation 7)}$$

$$Volume_{segment} = \pi h\left(\frac{R^2 + Rr + r^2}{3}\right) \qquad \text{(Equation 8)}$$

$$Volume_{total} = \sum Volume_{segments} \qquad \text{(Equation 9)}$$

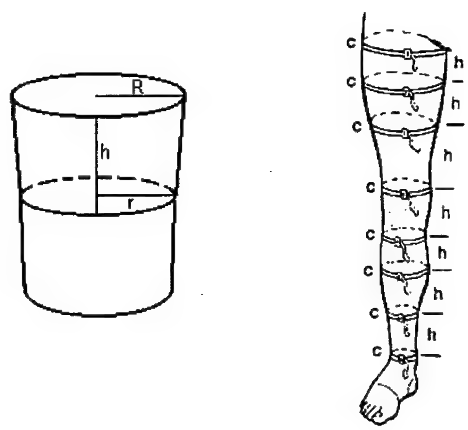


Figure 1. Volume estimation by serial truncated cones. (Adapted from Thornton et al. [70])

The plethysmograph used in this study, the Anthropometric Sleeve Plethysmograph (ASP) consisted of 9 horizontal tapes running through fixed apertures in two nondistensible axial index strips. The horizontal tapes were separated by 6 cm intervals (10 cm at the knee). The axial strips were taped medially and laterally on the subjects right leg, to keep the circumferential tapes parallel and stable. Great care was taken during the measurement process to avoid skew. Measurements, taken at 5-minute

intervals, were made against a metal friction bracket to 0.5 mm using a tensiometer to ensure consistency. These individual data are presented in Appendix B. Only volumes for the calf and lower two thirds of the thigh were measured, as the upper third of both thighs were instrumented with venous occlusion cuffs. While this restricted volume measurement will influence reported total leg volumes, it should have minimal effect on percent change in leg volume.

The ASP system did not incorporate an elastic stocking foundation as described by Thornton et al. (70), which could potentially apply circumferential pressures to the leg, thereby artificially reducing the volume measurements. The error introduced by assuming that the human leg is shaped like a series of perfect cones is minimized by the large number of segments and circumferential measurements used. Use of this method also assumes that 1) the measured circumference is circular, 2) that it maintains this same shape during volume changes, and 3) the changes are small, all of which are generally true (86). The ASP, unlike strain gauge plethysmography, provided absolute volume measurements, from which percent change could be calculated. Individual percent leg volume change data are presented in Appendix A.

A dual strand, mercury-in-silastic strain gauge (Medasonics, Fremont, CA) was placed around the maximal girth of the left calf. This plethysmography method, first used by Whitney in 1953, correlates leg volume changes with the changes seen in one plane of the maximal calf girth (86). The basis for this method is as follows (53).

The initial circumference of the calf is equal to the initial length (L_0) of the strain gauge. This initial length is related to initial calf radius by the equation for the circumference of a circle.

$$L_0 = 2\pi R_0 \qquad \textit{(Equation 10)}$$

Changes in leg volume that occur after microgravity or tilt-induced fluid shifting will change the radius of the limb cross-section to R_1 with a concomitant change in strain gauge length to L_1. The change in length (ΔL) is reflected in the equation:

$$\Delta L = 2\pi\Delta R \qquad \textit{(Equation 11)}$$

$$\text{where } \Delta R = R_1 - R_0 \qquad \textit{(Equation 12)}$$

The change in the cross-sectional area of the limb then is calculated by:

$$\Delta A = \pi\left(R_1^2 - R_0^2\right) \qquad \textit{(Equation 13)}$$

If Equation 12 is substituted into Equation 13 where $R_1 = \Delta R + R_0$ then:

$$\Delta A = \pi\left[2R_0\Delta R + (\Delta R)^2\right] \qquad \textit{(Equation 14)}$$

Changes in R are generally very small, so $(\Delta R)^2$ can be excluded, resulting in:

$$\Delta A = 2\pi R_0 \Delta R \qquad \textit{(Equation 15)}$$

Substituting in Equations 10 and 11 results in:

$$\Delta A = \frac{L_0 \Delta L}{2\pi} \qquad \textit{(Equation 16)}$$

Finally, percent change in cross-sectional area (assumed to be proportional to percent change in leg volume) is calculated by dividing both sides by A which yields:

$$\frac{\Delta A}{A} = \frac{2\Delta L}{L_0} \qquad \textit{(Equation 17)}$$

With the strain gauge, as the circumference of the calf changes with volume, the silastic tube changes in length, causing concurrent resistance changes across the mercury column (52,86). The continuous voltage/resistance measurements were calculated by the

computer to percent change in circumference. Strain gauge data were digitized continuously at a sampling frequency of 1 Hz with a 286-based microcomputer (SupersPort, Zenith, St. Joseph, MI) using data acquisition hardware (DAS-20, Metrabyte, Taunton, MA) and software (Labtech Notebook, Wilmington, MA). Strain gauge data were desampled by half, and a 30 unit moving average was applied to eliminate noise (Microsoft Excel 7.0, Microsoft Corporation). These filtered individual data are shown in Appendix C. While this method provides continuous real-time output, it makes a number of assumptions. It utilizes the same geometric assumptions as the anthropometric method, i.e. the circumference of the leg is circular, it keeps the same geometrical shape, the increase is small, etc. However, this method also assumes that the circumference changes seen in the entire leg are identical to those seen in a single plane of calf tissue, and the potential error is inherently obvious. This being the case, statistical analysis of leg volume changes were performed on the more definitive anthropometric measurements, while a comparative study was performed to determine the appropriateness of using strain-gauge plethysmography as an index of leg volume changes.

Pneumatic occlusion cuffs were placed on the upper third of both thighs, as close as possible to Poupart's ligament. The cuffs remained loose until inflation to 50 mmHg, which was accomplished in a smooth and rapid manner with an air compressor/reservoir. The occlusive cuffs were connected by a common 'Y' valve so that pressures, which were monitored using both analog and digital output, remained equal throughout inflation (See Figure 2 for full instrument configuration). An occlusion pressure of 50 mmHg was chosen for a number of reasons. First of all, this is an occlusive pressure widely used by

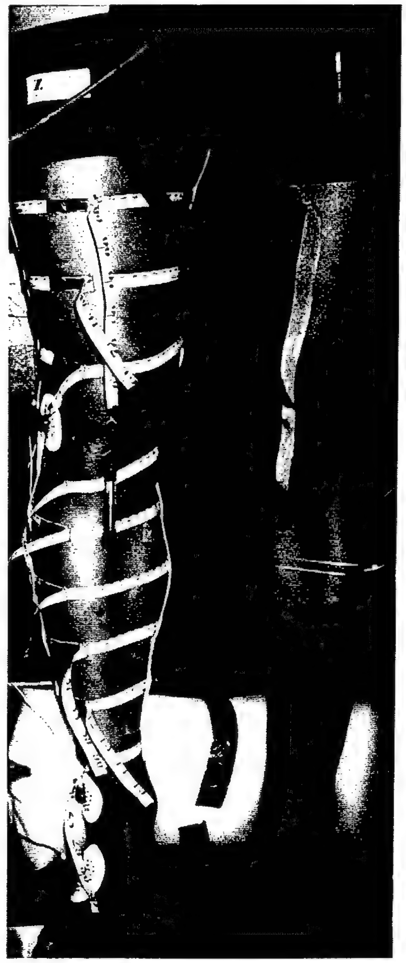


Figure 2. Full instrument configuration

researchers in compliance studies, and because it is below average diastolic blood pressure, it has been demonstrated to impede venous flow while leaving arterial flow unaffected (14,57,72). Secondly, venoconstrictive cuff research conducted by both Katkov et al. (47) and Gazenko et al. (26) evaluated cuff pressures of 40 mmHg and 60 mmHg. Utilizing an average of their values allows a comparison of results while investigating cardiovascular and volume changes at a previously unexamined pressure.

The subjects were instructed to remain as still as possible during data collection prior to which they were familiarized with the tilt table and protocol. The subjects wore

loose, nonconstrictive clothing and room temperature was maintained at ~25°C for all experimental runs.

Protocol. Anthropometric leg volume and hemodynamic data were taken after five minutes of quiet standing. The subject was then placed in the supine position on a motorized tilt table and secured with a canvas strap. Both heels were blocked 10 cm by foam pads to separate instrumentation from the table, and to reduce the small hydrostatic gradient that still remains in the legs of a supine subject (70). Anthropometric and hemodynamic data were taken every five minutes. After 30 minutes (6 intervals) in the supine position, during which the strain gauge plethysmograph was activated and zeroed, the subject was tilted to 90° vertical standing. After 10 minutes of standing, the subject was tilted back to the supine position. Thirty more minutes of supine exposure was followed by rotation to -12° head down tilt (HDT). After 30 minutes of HDT the venoconstrictive cuffs were inflated and maintained at 50 mmHg for 15 minutes. This was followed by cuff deflation and an additional 10 minutes of HDT. The subject was then rotated to 0° horizontal for 5 minutes as a safety precaution against syncope, and then to the standing position for a final 10 minutes. This tilt protocol is graphically illustrated below (Figure 3).

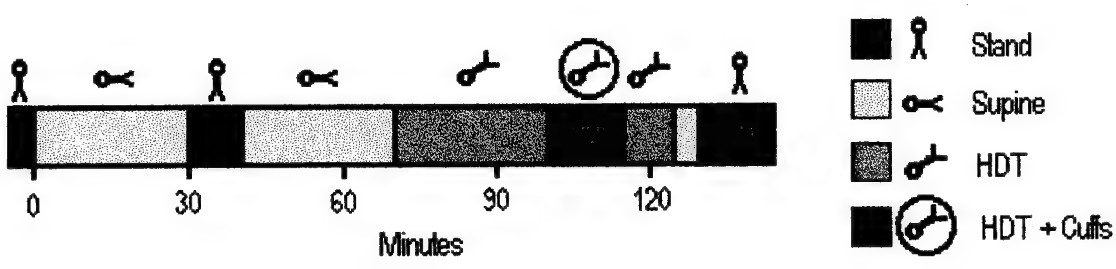


Figure 3. Graphic depiction of the tilt protocol

The -12° HDT model was used to simulate microgravity in this study (Figure 4). While -6° HDT is the current norm for modeling the physiological responses to microgravity, Thornton et al. (70) observed that no current HDT model even comes close to producing the magnitude of leg volume loss seen in space. Head down tilt studies utilizing -5 to -12° have yielded leg volume deficits of up to -5.6% while more extreme

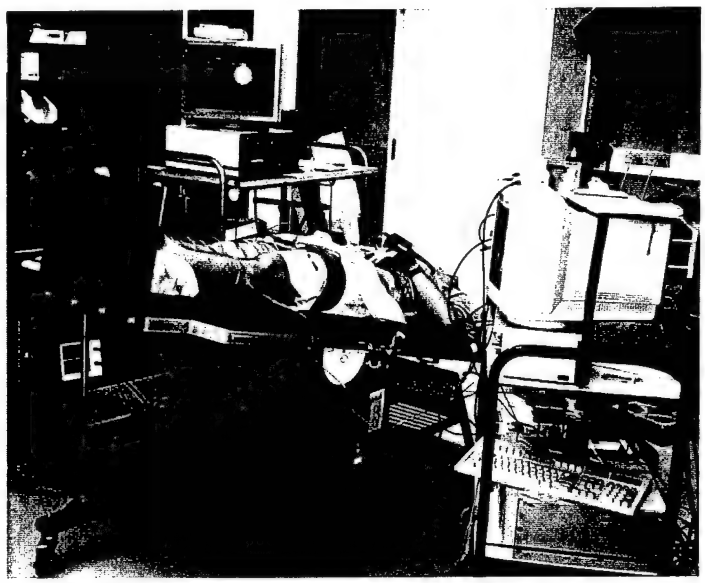


Figure 4. A subject being exposed to -12°HDT

tilts (-22°) caused -7.7% leg volume decreases (36,63,70). These tilt induced decreases are half of the -10-14% leg volume decreases seen in space (60). However, Convertino et al. (15) reported a 2% decrease in leg volume after 96 hours of -6° HDT while Panferova et al. (63) described a 2.5% leg volume deficit after only 4 hours of -12° HDT. While these differences are not dramatic, and there are conflicting data as to whether tilts ranging from 0° to -12° HDT result in significantly greater leg volume deficits, it does suggest that the -12° HDT causes greater fluid shifts. Additionally, Kakurin et al. (44) demonstrated that -12° HDT was a better model for reproducing microgravity-like responses than recumbent bedrest. Since the purpose of this study was intimately related

to altered fluid distributions and leg volume losses, the -12° HDT model was deemed the most likely to maximize leg volume losses, without the discomfort associated with the -22° HDT model, and therefore the most suitable. While this degree of tilt can still be unpleasant when experienced in long duration, the acute nature of the exposure limited subject discomfort.

Statistical Analysis. *Leg volumes and cuff efficacy.* Statistical analysis of all the data was performed on a 100 MHz Pentium (Intel Corporation, Santa Clara, CA) based microcomputer (ACT, Ft. Collins, Colorado) with Microsoft Excel (Microsoft Corp., Redmond, WA) Analysis ToolPak (Greymatter International, Inc., Cambridge, MA).

The ASP-measured percent change in leg volumes for all subjects (n=10) were averaged and graphed over time (Fig. 7). A relative zero for these data were obtained by averaging the supine leg volume values for all subjects and arbitrarily anchoring the percent change in leg volumes to this mean. For statistical analysis, averages of four 5-

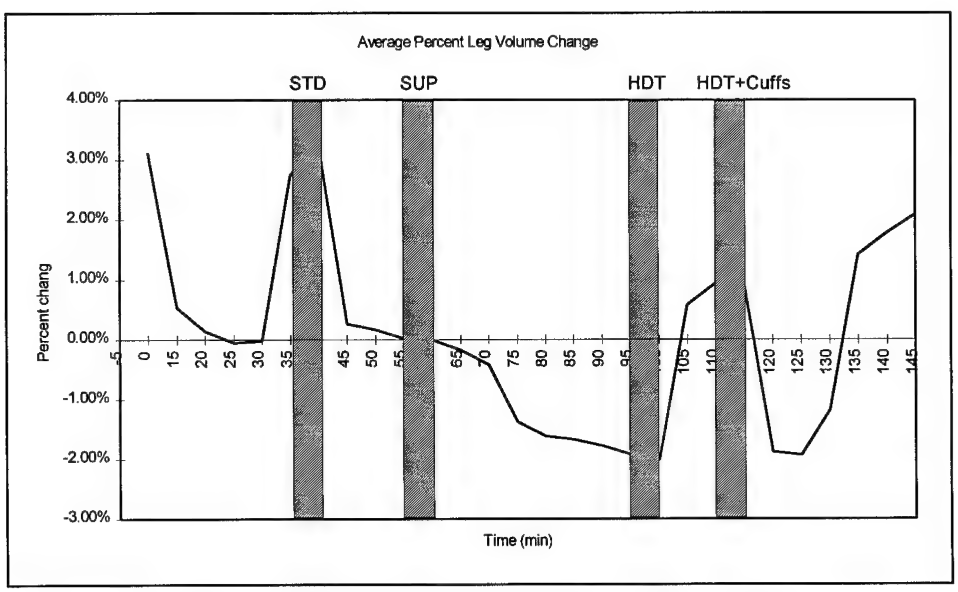


Figure 5. Intervals used for statistical analysis of volume changes

minute intervals (2 consecutive points) were computed. These four intervals represented the leg volumes for the different conditions applied in the protocol which were: Stand, Supine, HDT and HDT + the venoconstrictive cuff applied (HDT+Cuffs). The intervals are graphically identified in Figure 5.

An analysis of variance determined the significance of differences in leg volumes, followed by Tukey's post-hoc test to determine where the differences existed. A significant difference in HDT and HDT+Cuffs leg volumes would be interpreted as a positive change in fluid distribution and a successful employment of the thigh cuffs.

Comparison of plethysmography methods. Percent volume change data collected with the ASP were compared to data collected with the strain gauge plethysmograph. In order to perform the comparison, eight intervals (Stand 1 (STD1), Supine 1 (SUP1), Supine 2 (SUP2), HDT 1, HDT 2, HDT 3, HDT+Cuffs and HDT 4) were selected to represent the percent leg volume change value for significant stages of the protocol (See

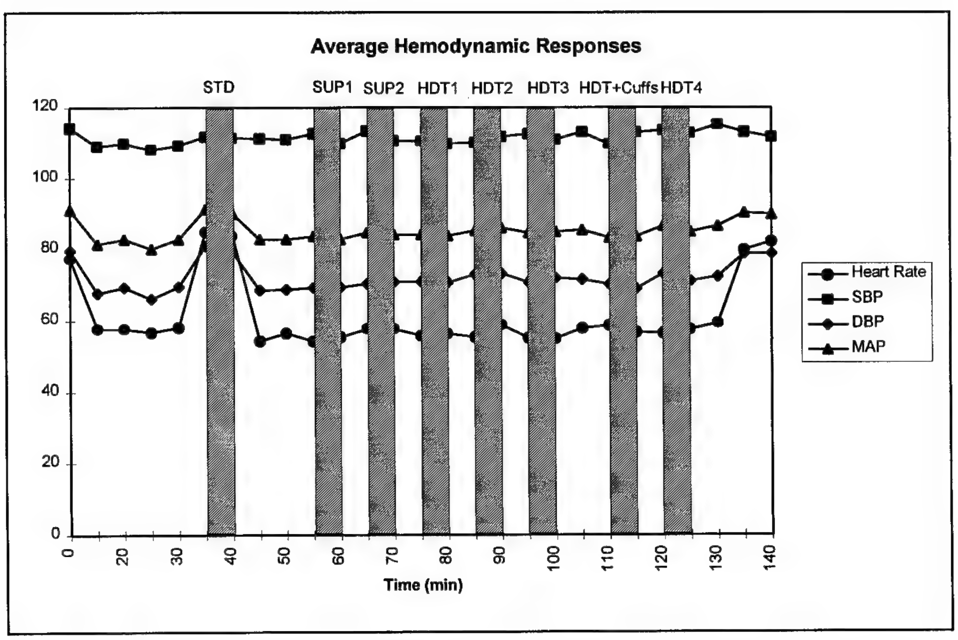


Figure 6. Intervals used for statistical analysis of ASP-strain gauge data and hemodynamic data

Figure 6 for graphic depiction of intervals). For the anthropometric measurements, each interval represented the average of two measurements (five minutes apart), while in the strain-gauge measurements, the interval represented the average of five minutes of continuous data. Due to poor strain-gauge data collected in one subject, only nine sets of data were evaluated (n=9). Paired two-tailed student t-tests were performed between ASP and strain-gauge values for corresponding intervals. A validation of the null hypothesis (no significant difference between measurements) would be interpreted to establish strain-gauge plethysmography as a viable method for measuring change in leg volume. A correlation/regression was also performed with the strain gauge and ASP data to substantiate the t-test results.

Hemodynamic changes. Hemodynamic data (HR, SBP, DBP) were collected and averaged (n=10). These data were divided into eight 5-minute intervals in the same manner described for the plethysmograph comparison, resulting in interval averages for STD, SUP1, SUP2, HDT 1, HDT 2, HDT 3, HDT+Cuffs, HDT4 (Figure 6). An ANOVA was performed on all intervals. Since this tilt protocol incorporated a NASA Operational Stand Test (29 min supine, 10 min stand) at the outset, the resultant measurable and significant hemodynamic changes were used to assess the sensitivity of the measurement methods. A second ANOVA was then performed, excluding the STD interval to determine whether there were any other significant hemodynamic changes for the duration of the protocol. Validation of the null hypothesis would be interpreted as the cardiovascular systems ability to regulate arterial pressure without compromise for the duration of the protocol, and the inability of venoconstrictive cuffs to modify hemodynamic variables.

CHAPTER IV

RESULTS

The stand-supine, supine-HDT and HDT-HDT+Cuffs leg volumes were all significantly different ($p<0.01$). While application of the venoconstrictive cuffs caused leg volumes to trend toward values exceeding those seen even in the supine position, these volumes (Supine-HDT+Cuffs), however, were not significantly different (Fig. 7).

Postural Leg Volume Changes. An average of 162 ml (3.00% increase in leg volume) of fluid shifted down to the instrumented leg during standing. This equates to about 300 ml of total fluid movement to both legs when moving from supine to standing. Meanwhile exposure to -12° HDT caused a mean 106 ml volume (-1.97%) deficit in one leg, ~200 ml total. These data taken together demonstrate an approximate loss of 0.5 liters of fluid (-4.97%) from both of the legs in the transition from standing to the -12° HDT position (Table 1).

Table 1. Volume and Percent Volume Change Data (note: the knee segment was not included in the thigh and calf calculations; mean±S.D.).

Interval	Avg. Absolute Leg Vol. (ml)	Avg. Vol.Δ from Supine	%Δ from Supine	%Δ in Thigh Vol.	%Δ in Calf Vol.
Stand (STD)	5664±733	162±44	3.00±0.96	3.06±1.30	3.08±0.68
Supine (SUP)	5501±729	-1±13	0±0.26	-0.06±0.29	-0.04±0.42
HDT	5397±745	-106±50	-1.97±1.04	-2.06±1.12	-2.10±0.99
HDT+Cuffs	5553±744	51±50	0.94±0.97	1.52±1.17	0.44±0.92

Cuff-Induced Leg Volume Changes. The inflation of venoconstrictive thigh cuffs to 50 mmHg significantly increased leg volumes from the -1.97% seen in -12° HDT to

0.94%, an overall 2.91% increase. This percent increase in leg volume is essentially identical to the 3.00% increase seen with moving from supine to standing. Initially diminished outflow caused by the venous occlusion resulted in 157 ml of volume to be restored to the ASP-instrumented leg, suggesting a total shift of ~300 ml to the legs.

Calf and Thigh Volume Changes. The percentage of volume change measured in the calf and thigh were essentially identical for all intervals except during cuff inflation (Table 1). Calf volume increased only 2.5% while thigh volume increased an average of 3.6%. An assessment of whether the thigh or calf contributed more to total volume changes was not undertaken due to the restricted nature of the volume measurements. Since only the lower two-thirds of the thigh were compared to the whole calf, the results of this analysis would have been skewed.

Table 2. Comparison Between Anthropometric and Strain Gauge Measurements.

Interval	ASP Measurements (% Leg vol. Δ)	Strain Gauge (% Leg vol. Δ)	p value
Stand (STD)	3.36±0.99	3.04±1.01	0.57
Supine 1 (SUP1)	0.18±0.48	-0.05±0.22	0.17
Supine 2 (SUP2)	-0.11±0.52	-0.36±0.26	0.21
HDT1	-1.67±0.74	-1.58±0.68	0.68
HDT2	-1.91±0.75	-1.84±0.86	0.82
HDT3	-2.09±0.83	-2.06±1.06	0.93
HDT+Cuffs	0.51±0.72	0.83±0.97	0.39
HDT4	-2.26±0.72	-2.00±1.23	0.54

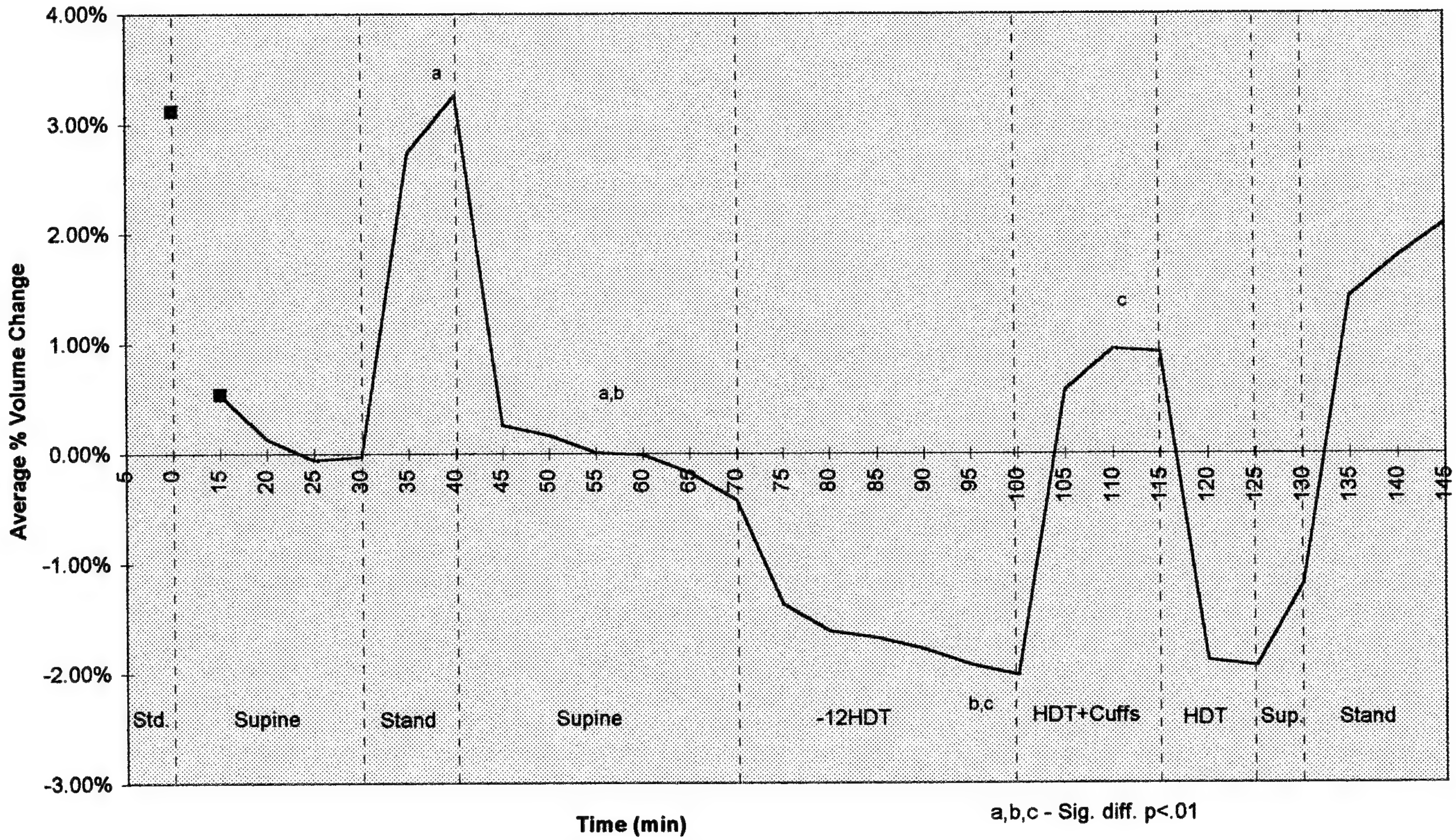
The measurements made by the Anthropometric Sleeve Plethysmograph (ASP) and the strain gauge plethysmograph were very similar and no significant differences were found ($p>0.05$) (Fig. 8 and Table 2). The strain gauge, however, seemed to measure greater volume changes than those made anthropometrically. A correlative/regression analysis demonstrated a significant positive relationship ($r=0.86$, $p<0.01$), supporting the

use of strain gauge plethysmography as a relatively accurate volume measurement tool (Fig. 9).

The hemodynamic variables measured during the stand interval were significantly different (except SBP) from those seen during the rest of the protocol ($p<0.01$). This attests to the sensitivity of instrumentation used to monitor hemodynamic changes. However, after the stand interval, there were no further significant changes in heart rate and blood pressure (Fig. 10).

The ASP...A Natural Plethysmograph

FIGURE 7
Average Percent Leg Volume Change (n=10)



*note: the first square marker represents the average of the first volume measurement. The second measurement was taken 15 min later and in 5 min intervals thereafter.

FIGURE 8

Comparison of Strain Gauge and Anthropometric Sleeve Measurements (n=9)

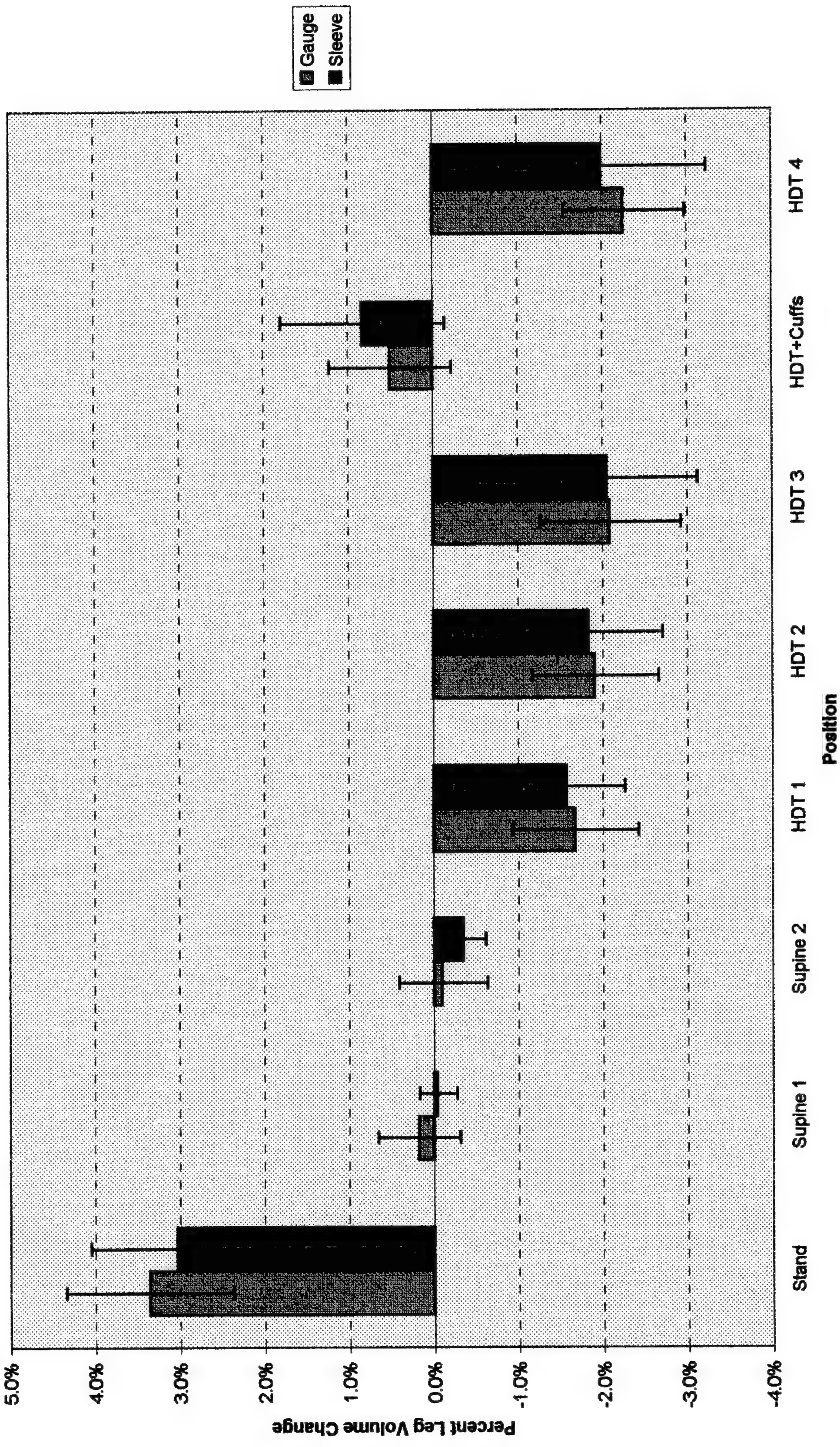


FIGURE 9

Anthropometric Sleeve - Strain Gauge Regression Analysis (n=9)

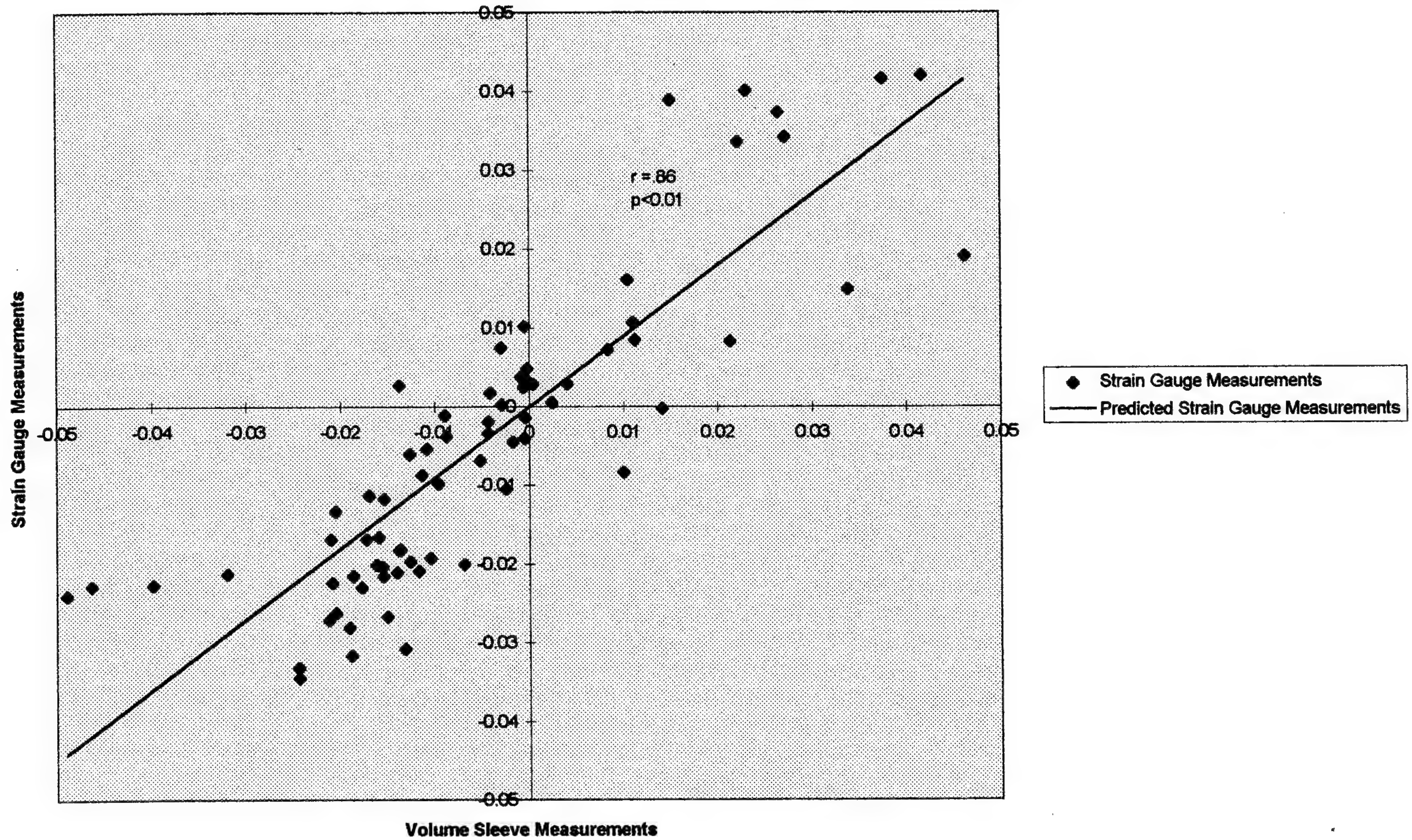
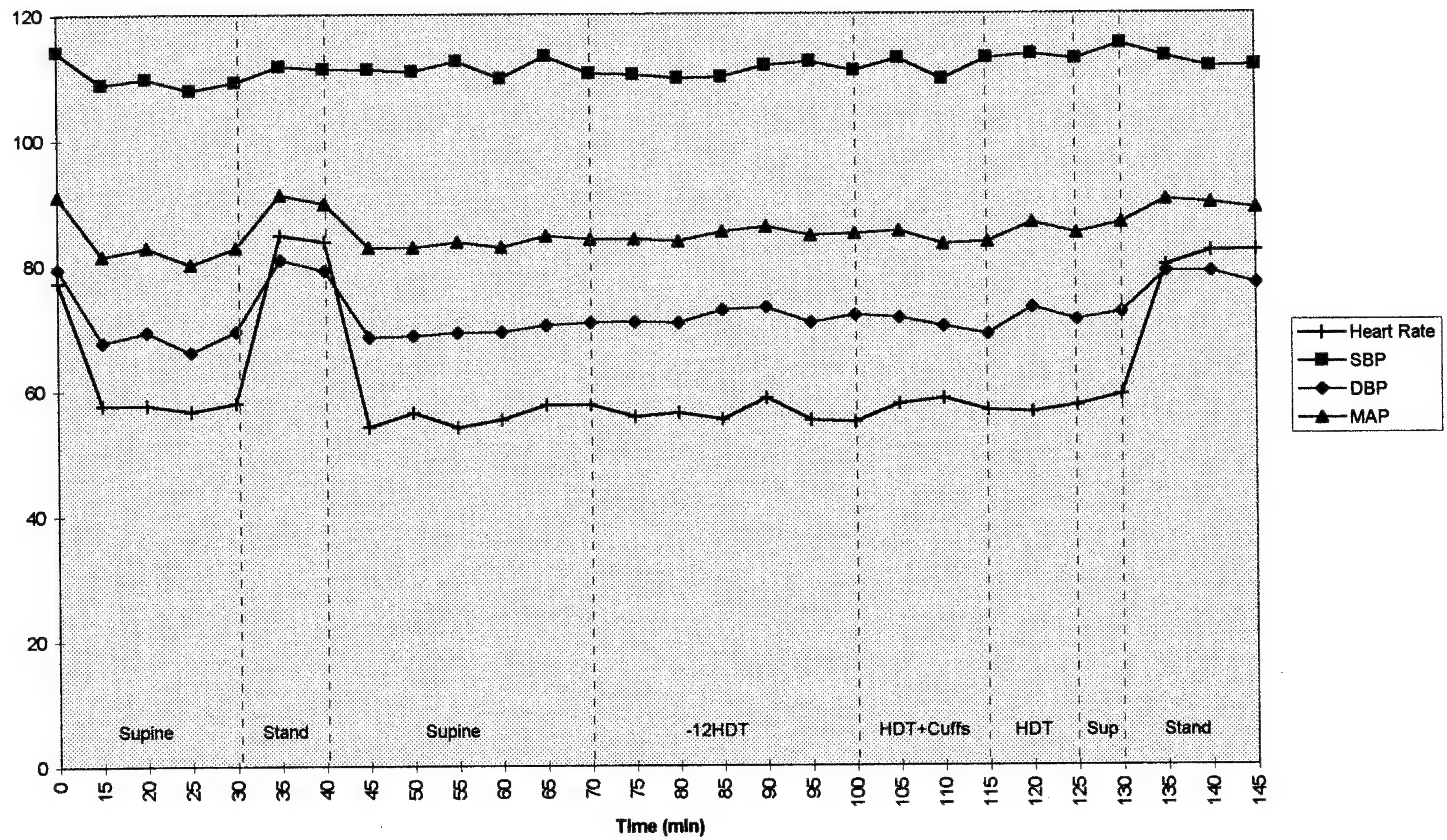


FIGURE 10

Average Hemodynamic Responses (n=10)



CHAPTER V

DISCUSSION

Results of research conducted in the late 1960's led investigators to discard venous occlusion cuffs as a potential countermeasure to cardiovascular deconditioning. In light of their specific research objectives, the decision to terminate this research direction in favor of other potential countermeasures was a logical one. Data from these ground studies and from spaceflight missions demonstrated little cardiovascular response to the inflation of both thigh and arm cuffs. Furthermore, the cuff protocols did not improve tolerance to post-study orthostatic challenge (79,81,82,83). The hemodynamic data obtained in this study corroborate previous studies. No significant cardiovascular responses (HR, SBP, DBP) were seen during the inflation of the venoconstrictive cuffs and this failure to elicit any measurable response, points to an inconsequential level of challenge.

Countermeasures are generally applied to fulfill one of two objectives. To be successful, the protocol must either significantly support or challenge the cardiovascular system, or both. Lower Body Negative Pressure was utilized in Skylab and early shuttle missions as an operational countermeasure. Negative pressure caused fluid to pool in the lower body, forcing the cardiovascular system to regulate arterial pressure and maintain cerebral perfusion (See Equations 1-3 recorded earlier in this document). This type of

challenge is intended to attenuate the deconditioning process, by maintaining baroreceptor viability and vascular smooth muscle tone, and to ultimately result in an increased tolerance to normal-g orthostasis. Exercise in space serves a similar role. A rigorous and consistent exercise program challenges the cardiovascular system to respond to an increased workload. In addition, Convertino et al. (17) recently demonstrated that a maximal bout of exercise increases plasma volume, and proposed that if accomplished prior to re-entry, the increases could support an otherwise volume-depleted crewmember.

This supportive aspect of exercise is also demonstrated by other countermeasures such as fluid loading or g-suits. Ingestion of isotonic saline prior to re-entry has been successfully used to support blood volumes in astronauts with microgravity-induced hypovolemia (11). Likewise, pressure garments such as the 'g-suit' assist in the maintenance of arterial pressures by establishing a viable fluid distribution in the upper body (67). Contrary to the role of 'challenging' countermeasures these 'supportive' countermeasures are not designed, or expected, to impede the deconditioning process, they are intended to aid the deconditioned system in the regulation of cardiovascular function.

The objectives, protocols and conclusions of previous venous occlusion research indicate that early investigators (78) were evaluating cuffs as a 'challenge' countermeasure only. When occlusive cuffs were not found to induce adequate challenge on the cardiovascular system, in an effort to slow microgravity-induced deconditioning, the whole idea was discarded. The goal of the present study, however, was to demonstrate the basis for potential use of venoconstrictive cuffs as a supportive

countermeasure, by serving as an adjunct to existing countermeasures, and as a possible remedy to the early symptoms of space adaptation syndrome.

Mechanism of Venoconstrictive Cuff Action. As the present study demonstrated, partial occlusion of the lower limb venous vasculature results in increased leg volumes due to a reduced venous outflow. While this seems intuitively obvious, and has been demonstrated with numerous compliance studies (9,14,15,16,57,72,85) the magnitude, time course and relative distribution of the fluid shift have not been fully appreciated. In addition, compliance studies often occlude venous flow immediately proximal to the knee, not at the proximal thigh, and utilize strain gauge plethysmography to measure volume and subsequently derived changes in compliance (14,15,16,72). While this study has demonstrated that strain-gauge measurements are a relatively accurate index of leg volume changes, absolute volume measurements cannot be made.

In their study describing the fluid shifts seen with various simulations of microgravity, Thornton et al. (70) employed volume-pressure curves to explain the mechanism and degree of fluid shifts seen during 1-g standing, 1-g supine and microgravity. Using various data describing peripheral venous pressure in the calf during standing (100 cmH_2O) (70) and in the ankle while horizontal (16 cmH_2O) (90), and assuming the peripheral venous pressure found in the arm while in microgravity (5-7 cmH_2O) (49) is a reasonable estimate of calf venous pressure, a volume-pressure curve can be charted against known calf volume changes for the same conditions (Fig. 11). The high compliance indicated by the steep slope of the low pressure section of the curve suggests that in microgravity, small external pressures applied to the tissue can result in

sizable volume changes (70). This application of pressure, then, is the fundamental premise for the use of venoconstrictive cuffs.

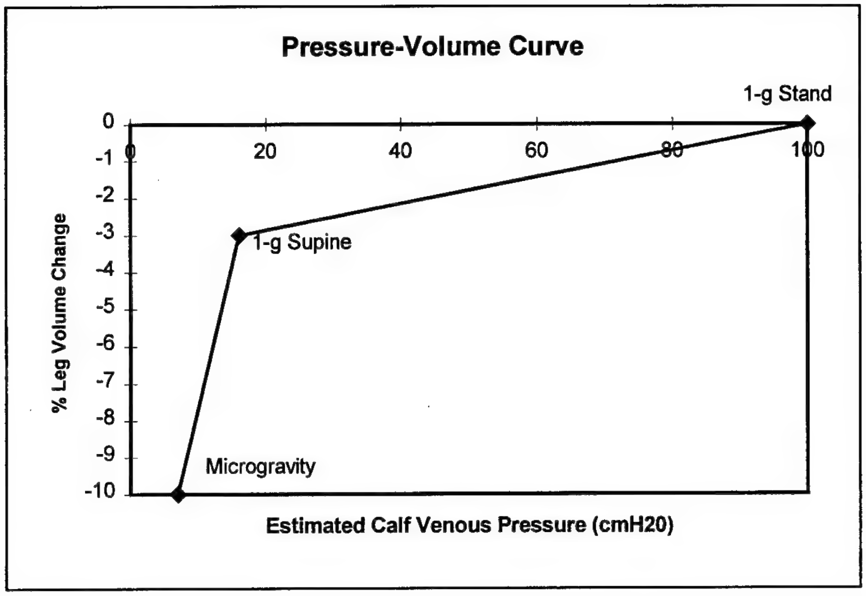


Fig. 11. Estimated pressure-volume relationship for the calf. (Adapted from Thornton et al. [70])

Inflation of the venoconstrictive cuffs causes only partial occlusion of the venous flow from the legs. Both Katkov et al. (47) and Gazenko et al. (26) suggested that the superficial veins are affected the most, while the deep veins remain relatively patent. External compression essentially 'removes' these superficial veins as a part of the viable circulation and the excess flow is handled by deep collateral circulation (26,47). While cadaver studies showed that external pressures of 200 to 400 mmHg were transmitted through the tissue to the core of the leg to occlude deep venous flow, only a fraction of those pressures were used in this and previous studies (18). Buckey et al. (10), on the other hand, demonstrated that the deep veins are responsible for 90% of volume changes seen with low (40 mmHg) occlusive pressures. Regardless, thigh cuff inflation results in increased leg volumes and a subsequent change in fluid distribution.

The fluid distribution achieved by the application of venoconstrictive cuffs is more 'earth-like' in that a significantly greater volume of blood resides in the legs. The similarities to 1-g fluid distribution, however, stop there. Use of the cuffs in simulated microgravity essentially divides the body into two compartments, with the lower compartment containing a greater percentage of the circulating blood volume than before. The fluid distribution seen in a standing individual, on the other hand, is a true gradient established by the hydrostatic component of the fluid column. Taken as a whole, the cuffs cause more volume to accumulate in the legs, yet the volume gradients within the respective compartments reveals how dissimilar they are to the total fluid distribution on Earth. The volumes in both compartments are still subject to resident forces, which in HDT is a component of the reversed hydrostatic gradient. So instead of one compartment (the whole body) with a reversed fluid distribution, the cuffs create two fluid compartments with reversed fluid distributions. This concept is presented in Figure 12.

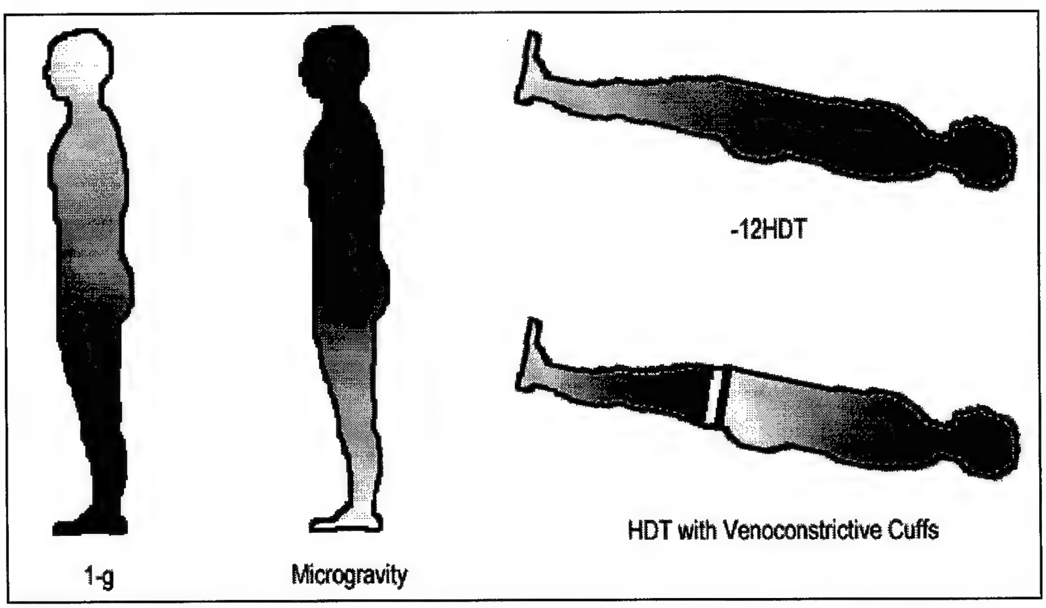


Figure 12. Relative fluid volume distributions under different conditions. Notice the similarities between Microgravity and -12°HDT. While leg volumes are increased, the overall fluid distribution seen with calf inflation is different from that seen in 1-g.

Data from this study substantiate the presence of this 'inverted' leg fluid distribution during occlusion. Cuff application caused greater volume increases in the thigh (+3.6%) than in the calf (+2.5%), demonstrating that even as the volume was accumulating, it was doing so in response to hydrostatic forces.

Venous occlusion caused an average 2.91% increase in leg volume from the starting HDT values. While the absolute volumes did not reach the values seen with standing, the relative change is comparable to the 3.00% leg volume increase when moving from supine to standing. One can speculate as to the reasons why the cuffs did not cause leg volumes to increase more than they did. First of all, the occlusive pressures used were not sufficient to completely occlude venous outflow. Higher pressures would have resulted in greater volume accumulations, as venous compliance studies have demonstrated, but the 50 mmHg used in this study provided sufficient fluid shifts with minimal subject discomfort.

Investigations conducted by Parazynski et al. (64) and Aratow et al. (2) found that during head down tilt microvascular flow of the upper body was not controlled as well as flow to the foot during the upright posture. This points towards a diminished capability to regulate flow/volume in the upper body. Likewise, Hinghofer-Szalkay et al. (37) found that plasma and blood density increased in subjects during -12° HDT as compared to the supine posture. Pressures in the peripheral compartments increase as the hydrostatic component increases with tilt. As these pressures increase, protein-rich plasma is forced from the vascular space causing a concomitant increase in blood density. These data indicate a net shift of fluid into the thoracocephalic extravascular space

resulting in the blood and plasma volume reductions seen during both real and simulated microgravity. Subsequently, when cuffs are applied, this diminished total volume may result in reductions in the volume of fluid trapped in the legs.

The relative changes in leg volume caused by cuff application in microgravity should be greater than those seen in ground based studies, such as the current study. Calf venous pressures seen in the normal 1-g supine position were higher than those estimated to exist in microgravity. Thornton et al. (70) suggested that this may be due to the weight of abdominal contents pushing on the venous vasculature, providing enough transmural pressures to maintain distal venous pressures. Removal of this weight in microgravity not only contributes to greater leg volume reductions, but also increases leg venous compliance as the cephalad fluid movement causes venous vasculature to shift to the steeper portion of the volume-pressure curve (Figure 11). Therefore, the pressures applied by the cuffs in microgravity should result in greater increases in leg volume than those seen on the ground.

Comparison to the Existing Literature. Leg volume changes seen with HDT in this study are comparable to those described by previous investigators. However, there is a tendency in previous studies to compare leg volume changes without establishing what posture was used for baseline measurements. Therefore, special care has been taken to report comparable percentage changes in the following discussion.

Standing to Supine comparisons. Thornton et al. (70) reported a 1.5% reduction in leg volume from standing measurements, after 30 minutes in the supine posture. An additional 60 minutes in the horizontal position resulted in a further 1% decrease. Panferova et al. (63) saw a 0.7% decrease in leg volume after 1 hour in the supine

position and -1.5% decrease after 2 hours. Data from this study suggest a slightly greater decrease (-2.91%) in volume when moving from standing to supine (after 30 minutes).

Supine to HDT comparisons. Thornton et al. (70) described no further significant leg volume changes when moving to -6° HDT after 30 minutes of supine posture. Panferova et al. (63), however, noted a 1% decrease in leg volume after 1 hour exposure to -12° HDT following 15 min of supine posture. Their data are similar to the present study, where exposure to 30 minutes of -12° HDT elicited a further 1.97% decrease in leg volume. Obviously, differences in the degree of HDT play a role in the magnitude of the fluid shifts.

Stand to HDT comparisons. The total magnitude of fluid shift seen in the present study was also comparable to that seen in previous investigations. Nixon et al. (62) saw a 5.0% reduction from standing total leg volume after 30 minutes of -5° HDT. Results from the present study are similar, with a 4.97% reduction in leg volume after 30 minutes of supine posture followed by another 30 minutes of -12° HDT.

Thigh and Calf comparisons. Thornton et al. (70) indicated that while a greater percentage of volume was lost from the calf than from the thigh during -6° HDT, the thigh lost relatively more volume in microgravity (60). Results from the present study demonstrated no significant difference in the percentage of volume lost from the calf and thigh during -12° HDT. Further comparisons are detailed in Table 3.

Time course of fluid shifts. While previous studies have described the magnitude of fluid shift during HDT, the earliest recorded volume changes were taken no earlier than 30 minutes after initiation of tilt. The present study describes the time course of

fluid shifts in 5-minute intervals. As seen in Figure 7, the majority of fluid shifting occurred after 5 minutes of supine exposure, following the transition from standing. When moving from supine to -12° HDT, 84% of the fluid shift had taken place after 10 minutes.

Table 3. Comparison of Previously Reported Leg Volume Changes. *note: this total volume measurement does not account for the top third of the thigh where the venoconstrictive cuff was located. (adapted from Thornton et al. [70])

Study	Condition	n	Measured Segment	Average Segment Volume (ℓ)	Time Course of Exposure (hours)	% Volume Δ from Supine	% Volume Δ from Stand
Nixon et al. (62)	5° HDT	6	Leg - single leg	7.5	0.5	-5.0	---
					2	-8.0	---
Hargens (36)	5° HDT	4	Calf - single leg	3.4	0.5	-5.6	---
Panverova et al. (63)	Horizontal	10	Leg - both legs	16.4	1	---	-0.7
					2	---	-1.5
					4	---	-1.8
	12° HDT	10	Leg - both legs	16.4	1	-1.0	---
					2	-1.0	---
					4	-2.5	---
	22° HDT	10	Leg - both legs	16.4	1	-4.3	---
					2	-5.8	---
					4	-7.7	---
Thornton et al.(70)	Horizontal	6	Calf - single leg	2.2	1.5	---	-4
			Thigh - single leg	6.0	1.5	---	-2
			Leg - single leg	9.3	.5	---	-1.5
					1.5	-2.5	---
	6° HDT	6	Calf - single leg	2.2	1.5	-1.5	---
			Thigh - single leg	6.0	1.5	0	---
			Leg - single leg	9.3	1.5	0	---
	Immersion	6	Calf - single leg	2.2	1.5	-3	---
			Thigh - single leg	6.0	1.5	-3	---
			Leg - single leg	9.3	1.5	-2.5	---
Lindgren	**12° HDT**	**10**	**Calf - single leg**	**2.4**	**.5**	**-2.1**	**-5.2**
			Thigh - single leg	**---**	**.5**	**-2.1**	**-5.1**
			Leg - single leg	**5.7***	**.5**	**-2.0**	**-5.0**
Thornton et al.(71)	Spaceflight (Skylab)	3	Calf - both legs	4.4	48	-9.0	---
			Thigh - both legs	9.9	48	-14.0	---
			Leg - both legs	15.4	48	-12.5	---
Moore et al. (60)	Spaceflight (Shuttle)	3	Calf - single leg	3.0	10	---	-6.0
			Thigh - single leg	5.1	10	---	-9.8
			Leg - single leg	8.1	10	---	-8.4

Potential Uses for Venoconstrictive Thigh Cuffs. There are a number of potential uses for venoconstrictive cuffs in an operational setting. Cuffs were employed by cosmonauts on Soyuz-38, reportedly reducing symptoms of space adaptation syndrome (dizziness, congestion and headaches) (56). While these symptoms are not life

threatening, they can impair on a crewmember's ability to conform to tight operational schedules. A reduction of the central volume should result in decreased cephalic volumes and pressures and in a subsequent reduction in congestion and edema. Some investigators have suggested that the initial fluid shift may play a role in Space Motion Sickness, and while this has been hypothesized to be unlikely, any potential for reducing the initial bouts of nausea and dizziness should be pursued (4,65). One might speculate that occlusive cuffs may lengthen the overall adaptation time, however, since reducing central and cephalic volumes should also reduce the magnitude of stimulation at centrally-located volume and pressure sensors. If this is the case, cuff use during the initial exposure to microgravity might represent a trade off between a short adaptation period characterized by acute discomfort, or a cuff-lengthened adaptation with diminished symptoms. Venoconstrictive cuffs could also be utilized prior to re-entry as an adjunct to existing countermeasures. The 'soak' protocol is a countermeasure regimen which utilizes fluid loading in conjunction with LBNP (67). With the elimination of LBNP from the current operational inventory, it is possible that venoconstrictive cuffs could serve as a replacement in potentiating fluid loading effectiveness. By sequestering a greater percentage of the plasma volume in the legs, the cuffs could cause the central volume to fall below its microgravity-adapted set point, allowing the newly acquired 'fluid loaded' volume to remain in circulation without inducing a compensatory diuresis. The venoconstrictive cuffs could essentially create more space in the vasculature for the ingested fluid. By keeping an increased volume in the lower compartments and away from the volume regulating stretch receptors in the upper body, the astronauts should be able to increase total fluid volumes in preparation for imminent orthostatic challenge.

Concerns with this Study. There were a number of areas in this study that could have benefited from closer attention.

1) The time course and application of conditions during the protocol could have been documented more accurately. While this had no effect on the results, it did require extensive backtracking through the strain-gauge data to ensure that comparison intervals were correctly aligned with corresponding ASP intervals.
2) Greater emphasis could have been placed on keeping the subjects from moving during the protocol. Movement caused considerable 'noise' in the strain gauge output. While the data were usable, filtering was required.
3) A leak in the pressure system caused the occlusive cuffs to leak slowly during the inflation period. The cuff pressures had to be nudged up two or three times, causing the occlusion pressure to fluctuate between 45 and 55 mmHg. While this should have had little impact on the overall results, an airtight pressure system would have been ideal.
4) Impedance plethysmography would have provided fluid shift data for the upper body, further corroborating the changes seen in the legs. Unfortunately, the system malfunctioned and the data were unusable. Availability of a backup system would have been preferable.
5) The low sampling rate (every 5 minutes) used to take hemodynamic data may have missed transient changes induced by any of the applied conditions. Continuous heart rate and blood pressure monitoring and data collection

would have better established any significant transient hemodynamic variability.

Future Research. While this study establishes a basis of information concerning the use of venoconstrictive thigh cuffs, only further research can establish their usefulness in an operational setting.

1) A HDT study should be conducted, during which measures of calf interstitial pressures and total plasma volume should be made during thigh cuff application to see how the lower body extravascular compartment is affected. If it is increased, it could point to a large volume reservoir for fluid loading.
2) A study should be conducted to assess the ability of venoconstrictive thigh cuffs to potentiate the effects of LBNP and exercise-LBNP.
3) A study should be conducted to determine the role of venoconstrictive cuffs in reducing fluid shifts during exposure to the pre-launch position.
4) A bedrest or HDT study should be conducted to determine what effects venoconstrictive cuffs have on fluid loading or other volutropic protocols. If greater plasma volumes are achieved, or if increased orthostatic tolerance is apparent, this combined countermeasure should be assessed in a flight setting.

CHAPTER VI

SUMMARY AND CONCLUSIONS

"I believe that this nation should commit itself, to achieving the goal, before this decade is out, of landing a man on the moon, and returning him safely to the Earth."

- PRESIDENT JOHN F. KENNEDY, 25 MAY 1961

No part of President Kennedy's historic challenge to the nation was more important than "returning him safely to the Earth." The priority embodied in these words remains with us today, as no mission, whether to low earth orbit or to Mars, can be a success if the crewmembers are not returned 'safely to the Earth.' Long duration exposure to microgravity has deleterious effects on the human body. The extent of bone and mineral loss, muscle atrophy, and cardiovascular deconditioning, brings into question whether planetary exploration-length missions can be endured by the crew. Despite intensive research in this arena, no method has been developed that completely preserves the human body from the rigors (or lack thereof) of long duration spaceflight.

The results of the present study have verified the initial hypothesis, that bilateral venoconstrictive thigh cuffs, applied at 50 mmHg during simulated (-12° HDT) microgravity, impede venous flow sufficiently to create a more 'Earth-like' fluid distribution. This hypothesis was verified by accomplishing the stated specific aims:

1. Leg volumes were measured (minus impedance plethysmography) and analyzed. A significant difference was found between leg volumes during HDT and HDT+Cuffs permitting the conclusion that the application of venocclusive cuffs can favorably alter the HDT fluid distribution.
2. Leg volume measurements were made at 5-minute intervals, allowing the time course of fluid shifts to be appreciated in a resolution not previously described.
3. The statistical and correlation/regression analysis performed on corresponding measurement data establish single-plane strain gauge plethysmography as a valid index of whole leg volume changes.
4. No significant cardiovascular changes were induced by cuff inflation, allowing a non-hypothesized conclusion that occlusive cuffs impart minimal challenge to the cardiovascular system.

The results of the present study demonstrate a potential avenue for further research and countermeasure therapy. Extensive research remains to be done in describing how the body responds to microgravity, and how to counter these responses. The small number of subjects and limited opportunities to investigate true microgravity, make ground studies invaluable in adding to the growing body of knowledge.

It is in this light that this study was conducted; to contribute a small amount of knowledge to the constellation of that which is known, in another small step towards the vastness of that which remains to be discovered.

REFERENCES

1. Alfrey CP, Udden MM, Leach-Huntoon C, Driscoll T, Pickett MH. Control of red blood cell mass in spaceflight. J Appl Physiol 1996; 81:98-104.

2. Aratow M, Hargens AR, Meyer JU, Arnaud SB. Postural responses of head and foot cutaneous microvascular flow and their sensitivity to bed rest. Aviat Space Environ Med 1991; 62:246-51.

3. Atkov OY, Bednenko VS. The system of the human organism in flight and during the readaptation period. In: Hypokinesia and Weightlessness: Clinical and Physiological Aspects. Madison, CT: International University Press. 1992; chapter 4, 241-329.

4. Barrett RJ, Lokhandwala MF. Circulatory and vestibular implications of central angiotensin mechanisms in physiological adaptation to weightlessness. Med Hypoth 1981; 7:1415-9.

5. Berne RM, Levy MN. The cardiovascular system. In: Berne RM, Levy MN. eds. Physiology, 3rd edition. St. Louis, IL: Mosby Year Book. 1993; chapter 29, 478-94.

6. Berry CA. View of human problems to be addressed for long-duration space flights. Aerospace Med 1973; 44:1136-46.

7. Buckey JC, Gaffney A, Lane LD, Levine BD, Watenpaugh DE, Wright SJ, Yancy CW, Meyer DM, Blomqvist CG. Central venous pressure in space. J Appl Physiol 1996; 81:19-25.

8. Buckey JC, Lane LD, Levine BD, Watenpaugh DE, Wright SJ, Moore WE, Gaffney FA, Blomqvist CG. Orthostatic intolerance after spaceflight. J Appl Physiol 1996; 81:7-18.

9. Buckey JC, Lane LD, Plath G, Gaffney FA, Baisch F, Blomqvist GC. Effects of head-down tilt for 10 days on the compliance of the leg. Acta Physiol Scand 1992; 144(S604):53-60.

10. Buckey JC, Peshock RM, Blomqvist CG. Deep venous contribution to hydrostatic blood volume change in the human leg. Am J Card 1988; 62:449-53.

11. Bungo MW, Charles JB, Johnson PC. Cardiovascular deconditioning during space flight and the use of saline as a countermeasure to orthostatic intolerance. Aviat Space Environ Med 1985; 56:985-90.

12. Cardus D. Effects of 10 days recumbency on the response to bicycle ergometer test. Aerospace Med 1966; 37:993-9.

13. Charles JB, Bungo MW, Fortner GW. Cardiopulmonary function. In: Nicogossian AE, Huntoon CL, Pool SL. eds. Space Physiology and Medicine, 3rd edition. Philedelphia, PA: Lea and Febiger. 1994; chapter 14, 286-304.

14. Convertino VA, Doerr DF, Flores JF, Hoffler GW, Buchanan P. Leg size and muscle functions associated with leg compliance. J Appl Physiol 1988; 64:1017-21.

15. Convertino VA, Doerr DF, Mathes KL, Stein SL, Buchanan P. Changes in volume, muscle compartment, and compliance of the lower extremities in man following 30 days of exposure to simulated microgravity. Aviat Space Environ Med 1989; 60:653-8.

16. Convertino VA, Doerr DF, Stein SL. Changes in size and compliance of the calf after 30 days of simulated microgravity. J Appl Physiol 1989; 66:1509-12.

17. Convertino VA. Exercise as a countermeasure for physiological adaptation to prolonged spaceflight. Med Sci Sports Exerc 1996; 28:999-1014.

18. Crenshaw AG, Hargens AR, Gershuni DH, Rydevik B. Wide tourniquet cuffs more effective at lower inflation pressures. Acta Orthop Scand 1988; 59:447-51.

19. Downie, N.M., Heath, R.W. Basic Statistical Methods. Third Edition. New York: Harper and Row, 1970.

20. Fritsch JM, Charles JB, Bennett BS, Jones MM, Eckberg DL. Short-duration spaceflight impairs human carotid baroreceptor-cardiac reflex responses. J Appl Physiol 1992; 73:664-71.

21. Fritsche-Yelle JM, Charles JB, Bennett BS, Jones MM, Eckberg DL. Short-duration spaceflight impairs human carotid baroreceptor-cardiac reflex responses. J Appl Physiol 1992; 73:664-71.

22. Fritsche-Yelle JM, Charles JB, Bennett BS, Jones MM, Eckberg DL. Spaceflight alters autonomic regulation of arterial pressure in humans. J Appl Physiol 1994; 77:1776-83.

23. Fritsch-Yelle JM, Charles JB, Jones MM, Wood ML. Microgravity decreases heart rate and arterial pressure in humans. J Appl Physiol 1996; 80:910-14.

24. Gauer OH. Orthostatic hypotension: closing remarks to session I. In: Denolin H, Demanet JC, eds. International symposium on neural control of the cardiovascular system and orthostatic regulation. Cardiology 1976; 61(Suppl I):91-2.

25. Gazenko OG, Genin AM, Yegorov AD. Summary of medical investigations in the USSR manned space missions. Acta Astronautica. 1981; 8:907-17.

26. Gazenko OG, Shumakov VI, Kakurin LI, Katkov VE, Chestukhin VV, Nikolayenko EM, Gvodev SV, Rumyantsev VV, Vasilyev VK. Effects of various countermeasures against the adverse effects of weightlessness on central circulation in the healthy man. Aviat Space Environ Med 1982; 53:523-30.

27. Gotshall RW, Yumikura S, Aten LA. Effect of the prelaunch position on the cardiovascular response to standing. Aviat Space Environ Med 1991; 62:1132-6.

28. Graveline DE. Maintenance of cardiovasular adaptability during prolonged weightlessness. Aerospace Med 1962; 33:297-302.

29. Greenleaf JE, Van Beaumont W, Bernauer EM, Haines RF, Sander H, Staley RW, Young HL, Usken JW. Effects of rehydration on $+G_z$ tolerance after 14-days bedrest. Aerospace Med 1973; 44:715-22.

30. Guell A, Braak L, Gharib C. Cardiovasular deconditioning during weightlessness simulation and the use of lower body negative pressure as a countermeasure to orthostatic intolerance. Physiologist. 1990; 33(Suppl. No. 1):S31-3.

31. Guell A, Braak L, Pavy-Le Traon A, Gharib C. Cardiovascular adaptation during simulated microgravity, lower body negative pressure to counter orthostatic hypotension. Aviat Space Environ Med 1991; 62:331-5.

32. Guell A, Tallarida G, Wegmann H. Physical countermeasures to be applied during long term manned space flight. European Space Agency. SP-1160. 1993.

33. Hargens AR, Tipton CM, Gollnick PD, Mubarak SJ, Tucker BJ, Akeson WH. Fluid shifts and muscle function in humans during acute simulated weightlessness. J Appl Physiol 1983; 54:1003-1009.

34. Hargens AR, Watenpaugh DE, Breit GA. Control of circulatory function in altered gravitational fields. Physiologist. 1992; 35:S80-3.

35. Hargens AR, Watenpaugh DE. Cardiovascular adaptation to spaceflight. Med Sci Sports Exerc 1996; 28:977-82.

36. Hargens AR. Fluid shifts in vascular and extravascular spaces during and after simulated weightlessness. Med Sci Sports Exerc 1983; 15:421-7.

37. Hinghofer-Szalkay H, Kenner T, Moser M. Short term gravity effects on volume homeostasis in man: assessment of transvascular fluid shifts after graded tilt. Physiologist. 1981; 24:S83-4.

38. Huntoon CL, Cintron NM, Whitson PA. Endocrine and biochemical functions. In: Nicogossian AE, Huntoon CL, Pool SL. eds. Space Physiology and Medicine, 3rd edition. Philedelphia, PA: Lea and Febiger. 1994; chapter 18, 334-50.

39. Huntoon CL, Whitson PA, Sams CF. Hematologic and immunologic functions. In: Nicogossian AE, Huntoon CL, Pool SL. eds. Space Physiology and Medicine, 3rd edition. Philedelphia, PA: Lea and Febiger. 1994; chapter 19, 315-62.

40. Johnson PC, Driscoll TB, LeBlanc AD. Blood volume changes. In: Johnston RS, Dietlein LF, eds. Biomedical results from Skylab. Washington, DC: NASA, 1977; SP-377:235-40.

41. Johnson PC. Fluid volume changes induced by space flight. Acta Astronautica. 1979; 6:1335-41.

42. Johnson RL, Nicogossian AE, Bergman SA, Hoffler GW. Lower body negative pressure: the second manned Skylab mission. Aviat Space Environ Med 1976; 47:347-53.

43. Jones PRM, Pearson J. Anthropometric determination of leg fat and muscle plus bone volumes in young male and female adults. Proc Royal Physiol Soc. 1969; 7:63-6P.

44. Kakurin LI, Lobachik VI, Mikhailov VM, Senkevich YA. Antiorthostatic hypokinesia as a method of weightlessness simulation. Aviat Space Environ Med 1976; 47:1083-6.

45. Kas'yan II, Talavrinov VI, Luk'yanchikov VI, Kobzev YA. Effect of antiorhtostatic hypokinesia and space flight factors on change in leg volume. Kosm Biol Aviakosm Med 1980; 4:51-5.

46. Katkov VE, Chestukhin VV. Blood pressure and oxygenation in different cardiovascular compartments of a normal man during postural exposures. Aviat Space Environ Med 1980; 51:1234-42.

47. Katkov VY, Chestukhin VV, Nikolayenko EM, Gvozdev SV, Rumyantsev VV. Effect of negative pressure and occlusion cuffs on intravascular pressure in legs of healthy man. Kosm Biol Aviakosm Med 1981; 15:9-12.

48. Kirsch K, Merke J, Hinghofer-Szalkay H. Fluid volume distribution within superficial shell tissues along body axis during changes of body posture in man. Pflug Arch 1980; 383:195-201.

49. Kirsch KA, Rocker L, Gauer OH, Krause R, Leach C, Wicke HJ, Landry R. Venous pressure in man during weightlessness. Science 1984; 225:218-9.

50. Leach CS, Alfrey CP, Suki WN, Leonard JI, Rambaut PC, Inners LD, Smith SM, Lane HW, Krauhs JM. Regulation of body fluid compartments during short-term spaceflight. J Appl Physiol 1996; 81:105-16.

51. Levick JR, Michel CC. The effects of position and skin temperature on the capillary pressures in the fingers and toes. J Physiol London 1978; 274:97-109.

52. Levitan BM, Montgomery LD, Bhagat PK, Zieglschmid JF. A comparison of limb plethysmograph systems proposed for use on the Space Shuttle. Aviat Space Environ Med 1983; 54:6-10.

53. Louisy F, Berry P, Marini JF, Guell A, Guezennec CY. Characteristics of the venous hemodynamics of the leg under simulated weightlessness: effects of physical exercise as countermeasure. Aviat Space Environ Med 1995; 66:542-9.

54. Luft UC, Loeppky JA, Venters MD, Greene ER, Eldridge MW, Hoekenga DE, Richards KL. Tolerance of lower body negative pressure (LBNP) in endurance runners, weightlifters, swimmers, and nonathletes. Albuquerque, NM: Lovelace Foundation, 1980; NASA Special Report NAS9-15483:1-35.

55. Luft UC, Myhre LG, Loeppky JA, Venters MD. A study of factors affecting tolerance to gravitational stress simulated by lower body negative pressure. Albuquerque, NM: Lovelace Foundation, 1976; NASA Special Report NAS9-14472:1-16.

56. Matsnev EI, Yakovleva IY, Tarasov IK, Alekseev VN, Kornilova LN, Mateev AD Gorgiladze GI. Space motion sickness: phenomenology, countermeasures, and mechanisms. Aviat Space Environ Med 1983; 54:312-7.

57. Melchior FM, Fortney SM. Orthostatic intolerance during a 13-day bed rest does not result from increased leg compliance. J Appl Physiol 1993; 74:286-92.

58. Montgomery LD, Hanish HM, Marker RA. An impedance device for study of multisegment hemodynamic changes during orthostatic stress. Aviat Space Environ Med 1989; 60:1116-22.

59. Montgomery LD. Body volume changes during simulated weightlessness: an overview. Aviat Space Environ Med 1987; 58(9, Suppl.):A80-5.

60. Moore TP, Thornton WE. Space Shuttle inflight and postflight fluid shifts measured by leg volume changes. Aviat Space Environ Med 1987; 58(9, Suppl.):A91-6.

61. Nicogossian AE, Sawin CF, Huntoon CL. Overall physiologic response to space flight. In: Nicogossian AE, Huntoon CL, Pool SL. eds. Space Physiology and Medicine, 3rd edition. Philedelphia, PA: Lea and Febiger. 1994; chapter 11, 213-27.

62. Nixon JV, Murray RG, Bryant C, Johnson RL, Mitchell JH, Holland OB, Gomez-Sanchez C, Vergne-Marini P, Blomqvist CG. Early cardiovascular adaptation to simulated zero gravity. J Appl Physiol 1979; 46:541-548.

63. Panferova NY, Kabesheva TA. Dynamics of fluid turnover in human extremities as related to different body positions. Kosm Biol Aviakosm Med 1987; 21:40-5.

64. Parazynski SE, Hargens AR, Tucker B, Aratow M, Styf J, Crenshaw A. Transcapillary fluid shifts in tissues of the head and neck during and after simulated microgravity. J Appl Physiol 1991; 71:2469-75.

65. Parker DE. Physiological and behavioral effects of tilt-induced body fluid shifts. Aviat Space Environ Med 1983; 54:402-9.

66. Prisk GK, Guy HJB, Elliott AR, Deutschman RA, West JB. Pulmonary diffusion capacity, capillary blood volume, and cardiac output during sustained microgravity. J Appl Physiol 1993; 71:15-26.

67. Sawin CF, Baker E, Black FO. Medical investigations and resulting countermeasures in support of 16-day Space Shuttle missions. J Grav Physiol P1-P9.

68. Schatz IJ. Orthostatic hypotension. Philadephia, PA: F.A. Davis Company. 1986; chapter 1, 1-11.

69. Shykoff BE, Farhi LE, Olszowka AJ, Pendergast DR, Rokitka MA, Eisenhardt CG, Morin RA. Cardiovascular response to submaximal exercise in sustained microgravity. J Appl Physiol 1996; 81:26-32.

70. Thornton WE, Hedge V, Coleman E, Uri JJ, Moore TP. Changes in leg volume during microgravity simulation. Aviat Space Environ Med 1992; 63:789-94.

71. Thornton WE, Hoffler GW, Rummel JA. Anthropometric changes and fluid shifts. In: Johnston RS, Dietlein LF, eds. Biomedical results from Skylab. Washington, DC: NASA, 1977; SP-377:330-8.

72. Thornton WE, Hoffler GW. Hemodynamic studies of the legs under weightlessness. In: Johnston RS, Dietlein LF, eds. Biomedical results from Skylab. Washington, DC: NASA, 1977; SP-377:324-9.

73. Thornton WE, Moore TP, Pool SL. Fluid shifts in weightlessness. Aviat Space Environ Med 1987; 58(9, Suppl.):A86-90.

74. Tipton CM, Greenleaf JE, Jackson CGR. Neuroendocrine and immune system responses with spaceflights. Med Sci Sports Exerc 1996; 28:988-98.

75. Tipton CM, Overton JM, Joyner MJ, Hargens AR. Local fluid shifts in humans and rats: comparison of simulation models with actual weightlessness. Physiologist. 1987; 3:S117-9.

76. Udden MM, Driscoll TB, Pickett MH, Leach-Huntoon CS, Alfrey CP. Decreased production of red blood cells in human subjects exposed to microgravity. J Lab Clin Med 1995; 125:442-9.

77. Vernikos J, Convertino VA. Advantages and disadvantages of fludrocortisone or saline loading in preventing post-spaceflight orthostatic hypotension. Acta Astronautica 1994; 33:259-66.

78. Vinograd SP, Manganelli LA. Literature summary on countermeasures. BSCP 72-01R. Biological Sciences Communication Project, The George Washington University Medical Center, Washington, D.C., 1972; 1:28-30.

79. Vogt FB, Johnson PC. Effectiveness of extremity cuffs or leotards in preventing or controlling the cardiovascular deconditioning of bedrest. Aerospace Med 1967; 38:702-7.

80. Vogt FB. Effect of extremity cuff-tourniquets on tilt table tolerance after water immersion. Aerospace Med 1965; 36:442-7.

81. Vogt FB. Effect of intermittent leg cuff inflation and intermittent exercise on the tilt table response after ten days bed recumbency. Aerospace Med 1966; 37:943-7.

82. Vogt FB. Plasma volume and tilt table response to water immersion deconditioning experiments using extremity cuffs. Aerospace Med 1967; 38:460-4.

83. Vogt, FB. Use of extremity cuffs as a cardiovascular reflex conditioning technique. Texas Institute for Rehabilitation and Research. Houston, Texas. NASA-CR-90248.

84. von Braun W. The Mars project. Urbana, IL: University of Illinois Press. 1952; 61-2.

85. Watenpaugh DE, Ballard RE, Breit GA, Bernauer EM, Blomqvist CG, Hargens AR. Calf venous compliance measured with head-up tilt equals supine calf compliance.

86. Whedon GD, Deitrick JE, Shorr E. Modification of the effects of immobilization upon metabolic and physiologic functions of normal man by the use of an oscillating bed. Am J Med 1949; 6:684.

87. White RJ, Leonard JI, Srinivasan RS, Charles JB. Mathematical modeling of acute and chronic cardiovascular changes during extended duration orbiter (EDO) flights. Acta Astronautica 1991; 23:41-51.

88. Whitney RH. The measurement of volume changes in human limbs. J Physiol 1953; 121:1-27.

89. Whitson PA, Charles JB, Williams WJ, Cintion M. Changes in sympathoadrenal response to standing in humans after spaceflight. J Appl Physiol 1995; 79:428-33.

90. Wood E, The veins. Boston, MA: Little Brown. 1965.

91. Yegorov AD, Itsekhovskiy OG. Study of cardiovascular system during long-term spaceflights. Kosm Biol Aviakosm Med 1983; 17:4-6.

APPENDICES

APPENDIX A

INDIVIDUAL ANTHROPOMETRIC SLEEVE FIGURES

*note: in the following charts, the first square marker represents the first volume measurement. The next measurement was taken 15 min later and in five minute intervals thereafter.

FIGURE A-1
% Leg Volume Change-Anthropometric Sleeve (Subject 1)

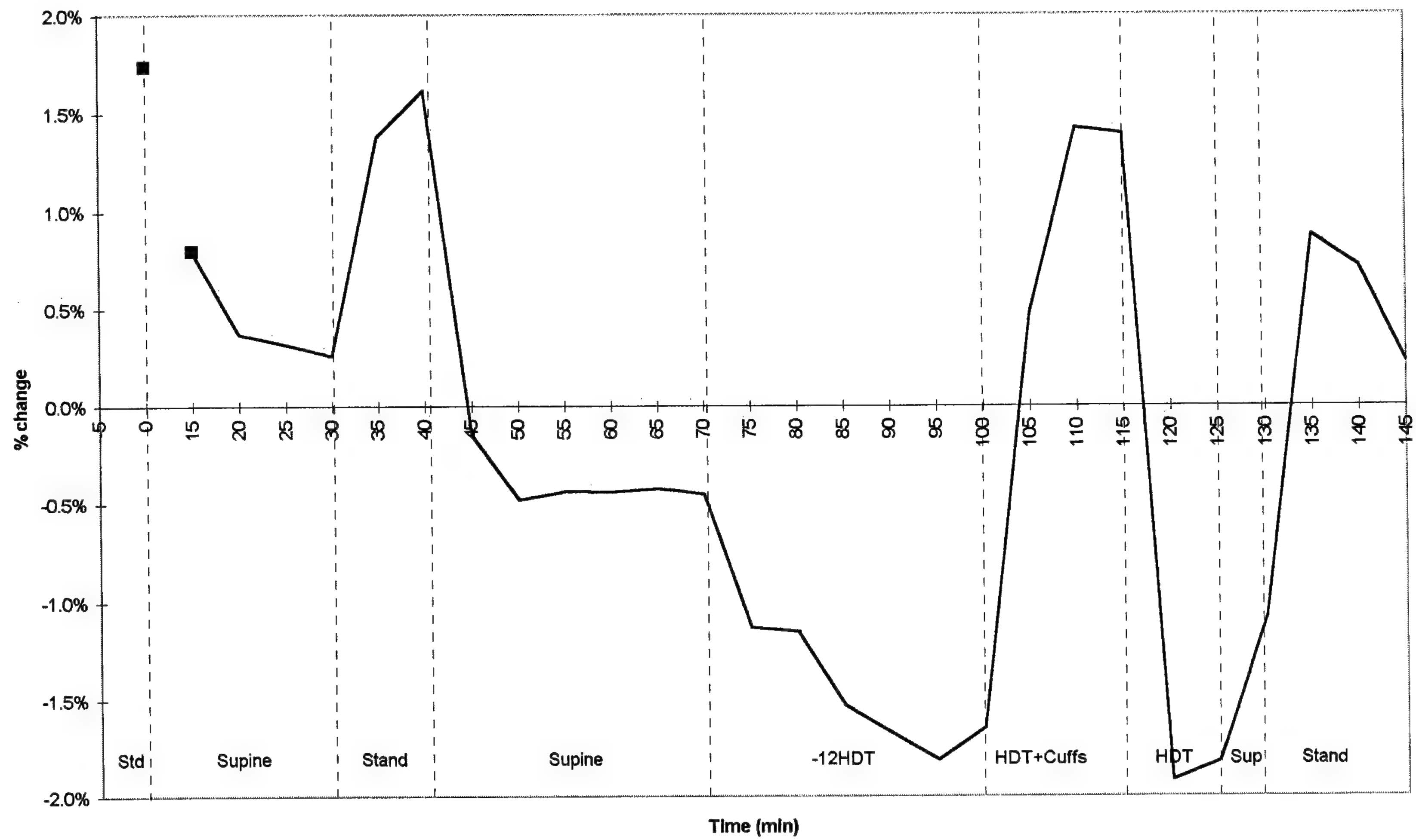


FIGURE A-2
% Leg Volume Changes-Anthropometric Sleeve (Subject 2)

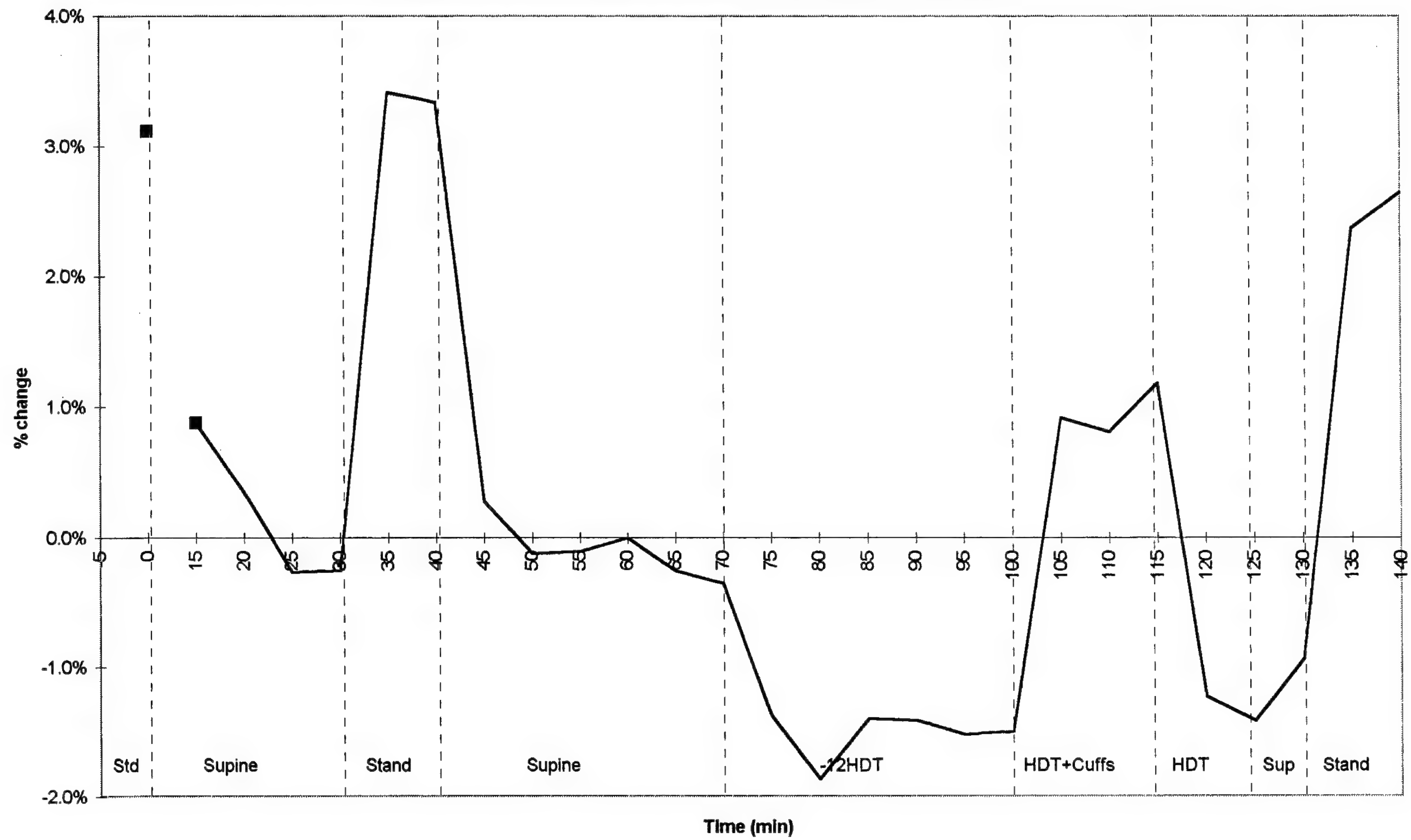


FIGURE A-3
% Leg Volume Change-Anthropometric Sleeve (Subject 3)

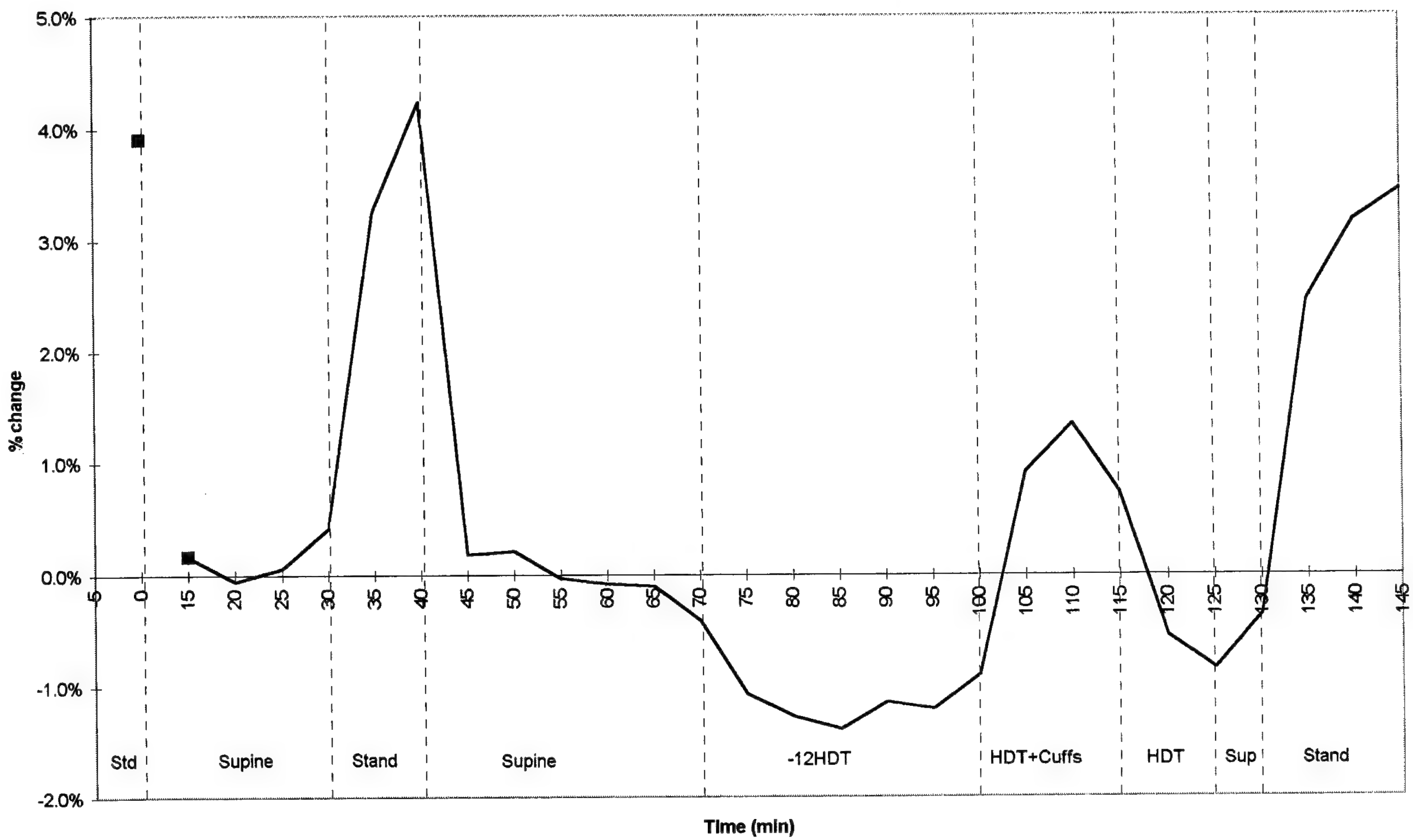


FIGURE A-4
% Leg Volume Change-Anthropometric Sleeve (Subject 4)

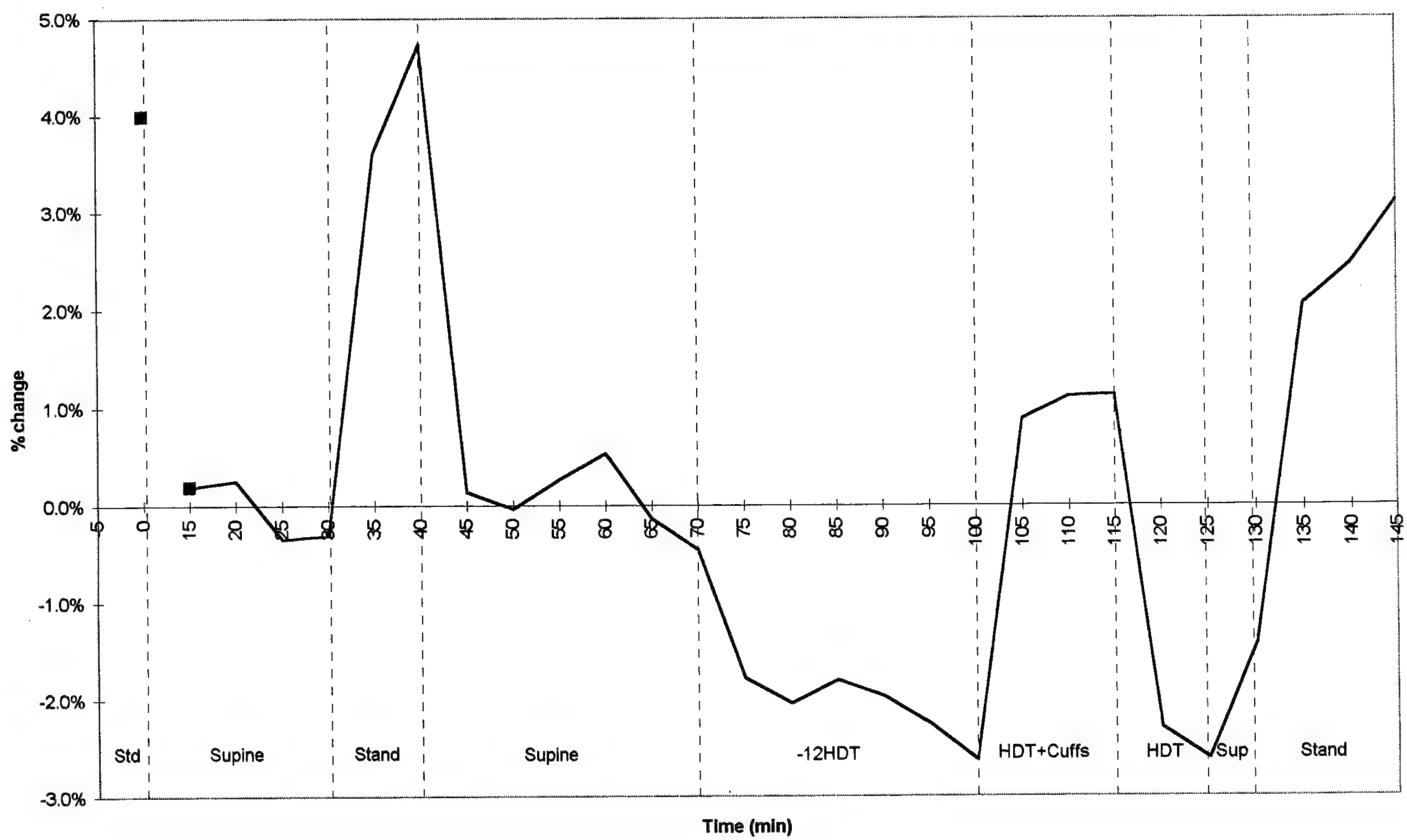


FIGURE A-5

% Leg Volume Change-Anthropometric Sleeve (Subject 5)

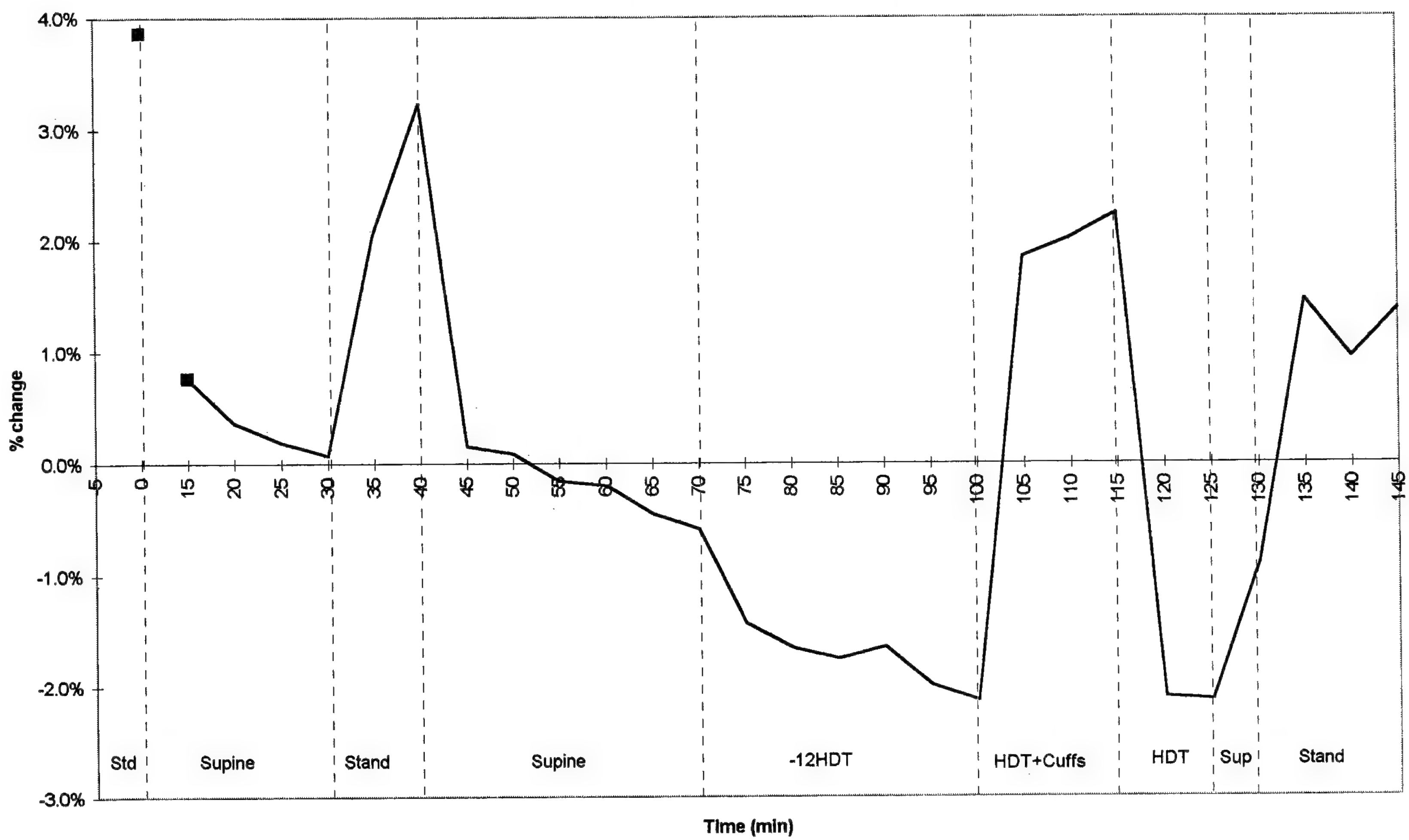


FIGURE A-6
% Leg Volume Change-Anthropometric Sleeve (Subject 6)

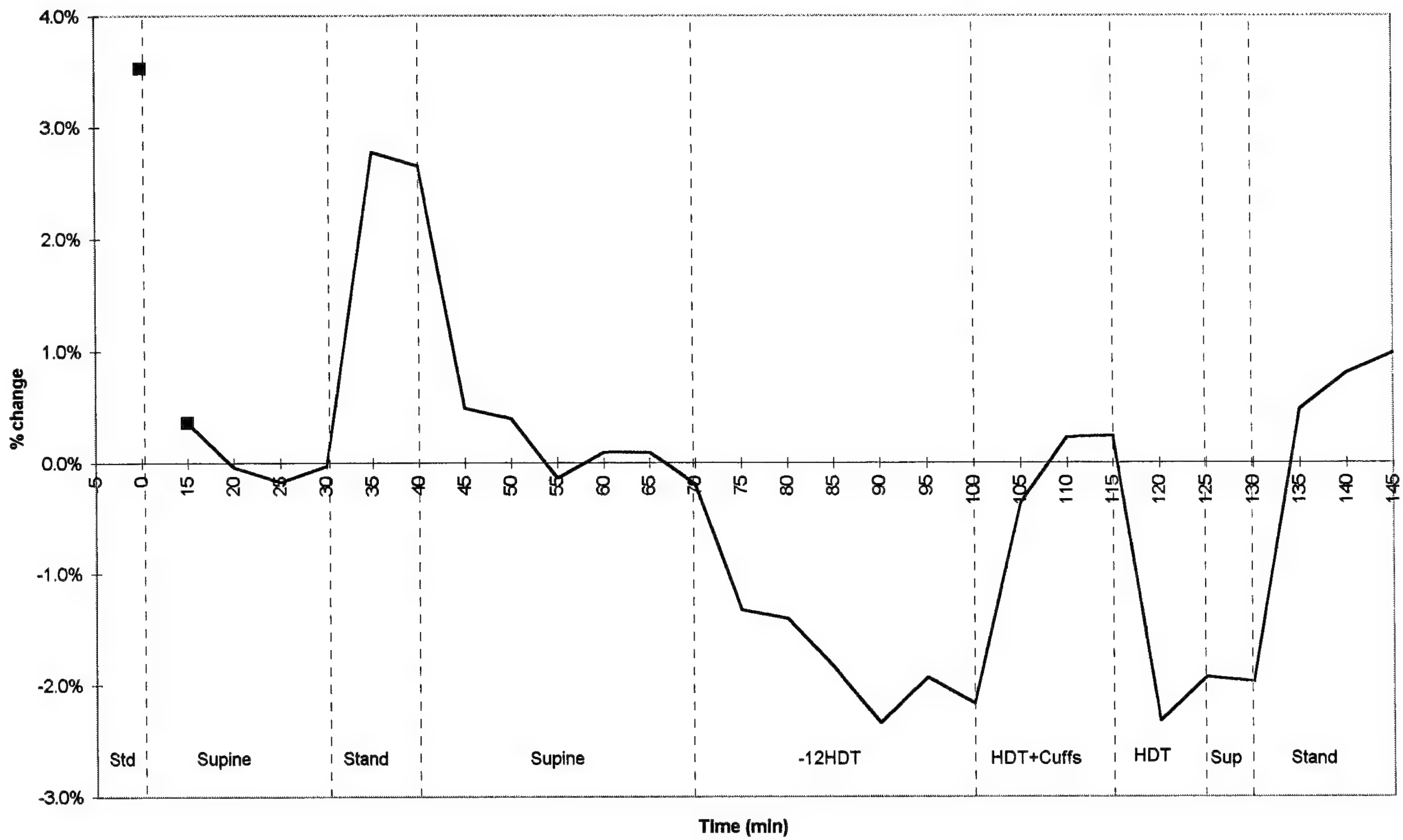


FIGURE A-7
% Leg Volume Change-Anthropometric Sleeve (Subject 7)

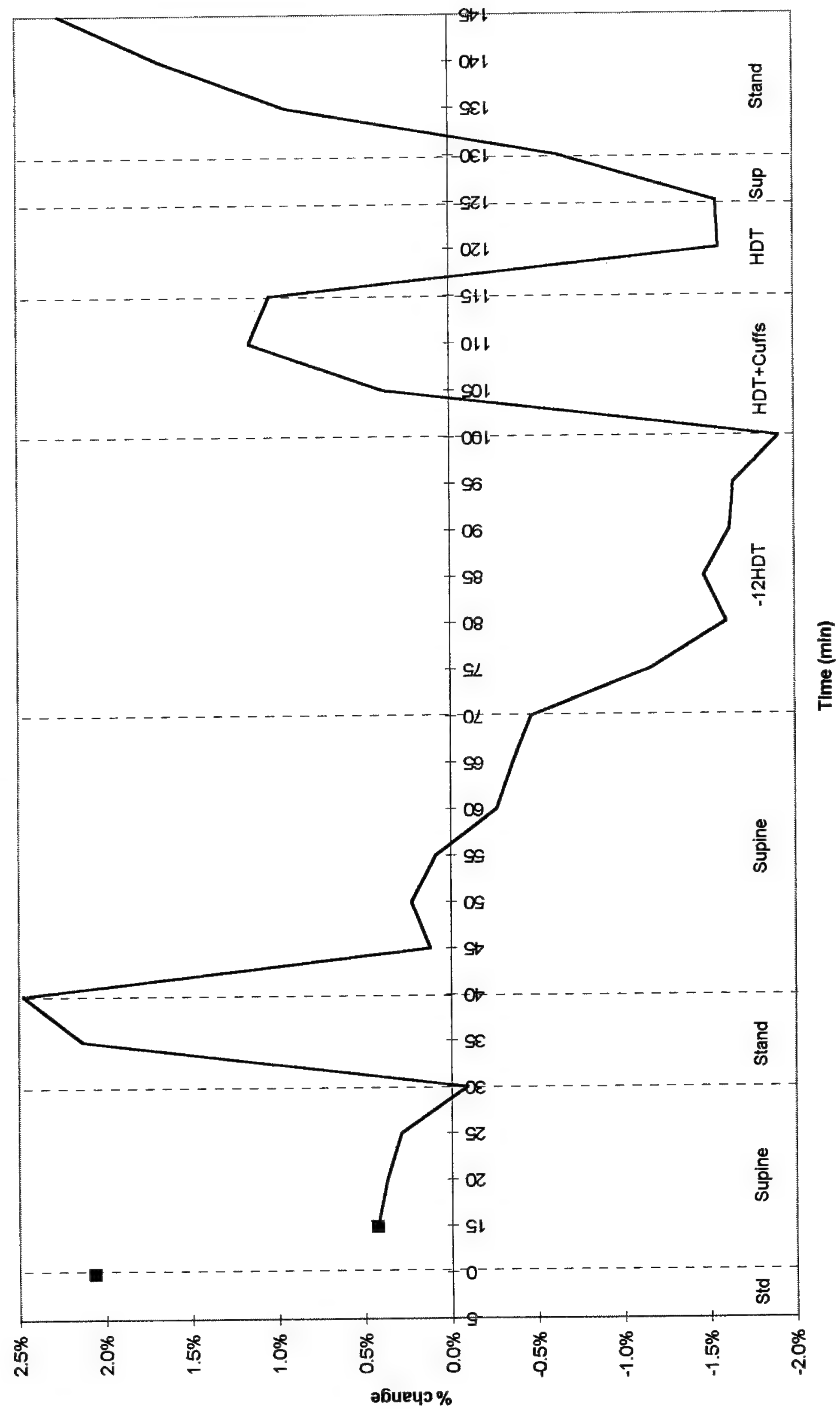


FIGURE A-8
% Leg Volume Change-Anthropometric Sleeve (Subject 8)

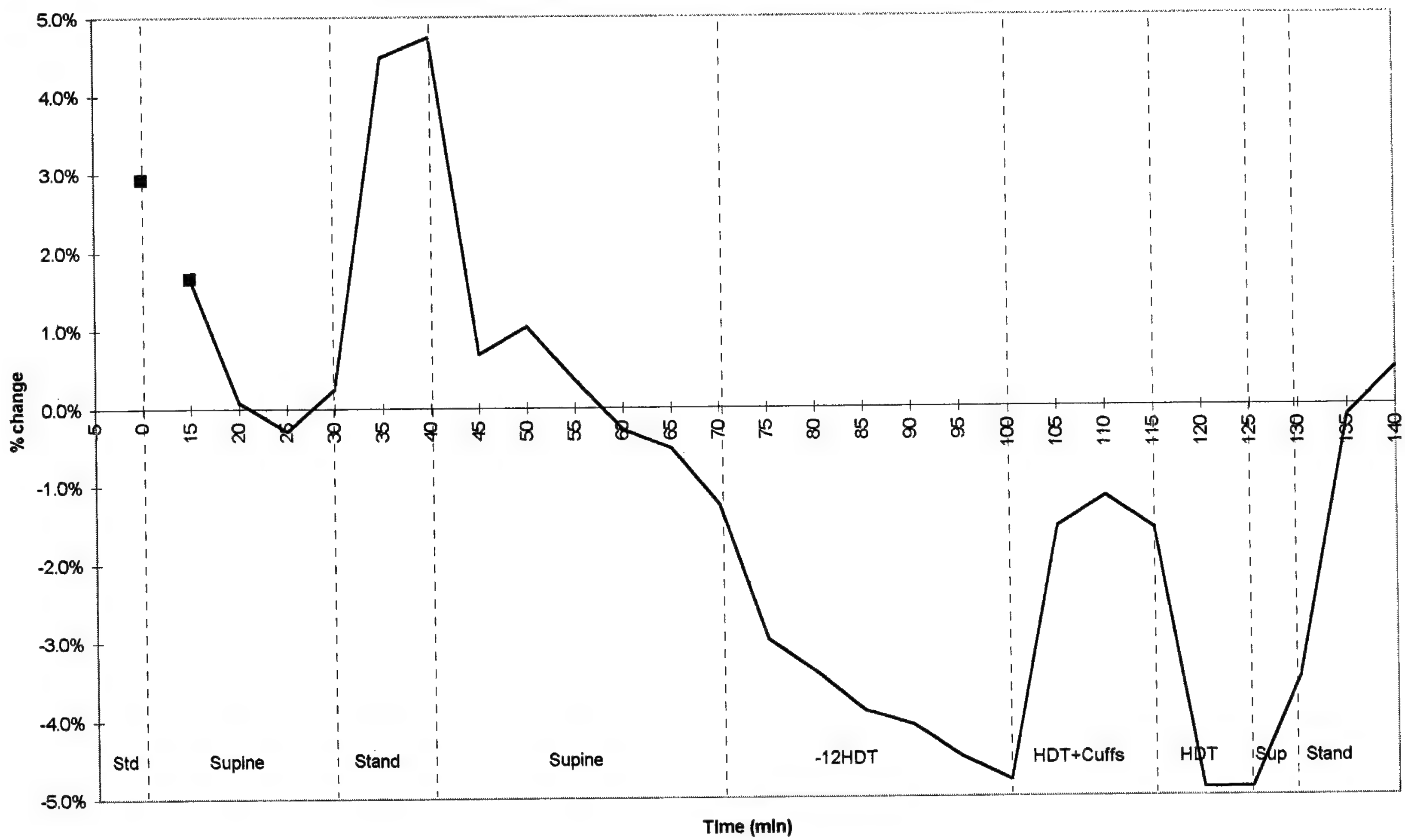


FIGURE A-9
% Leg Volume Change-Anthropometric Sleeve (Subject 9)

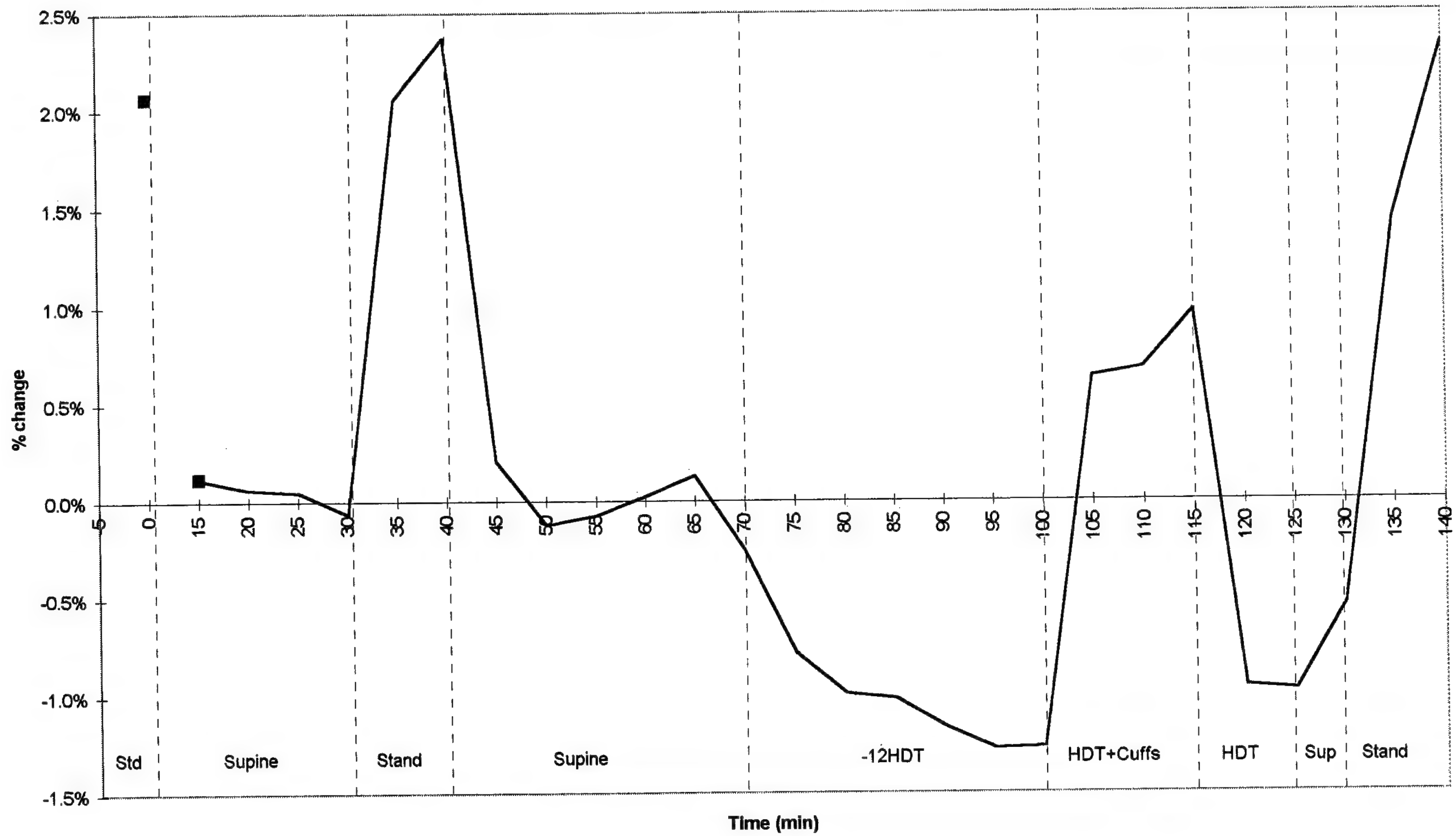
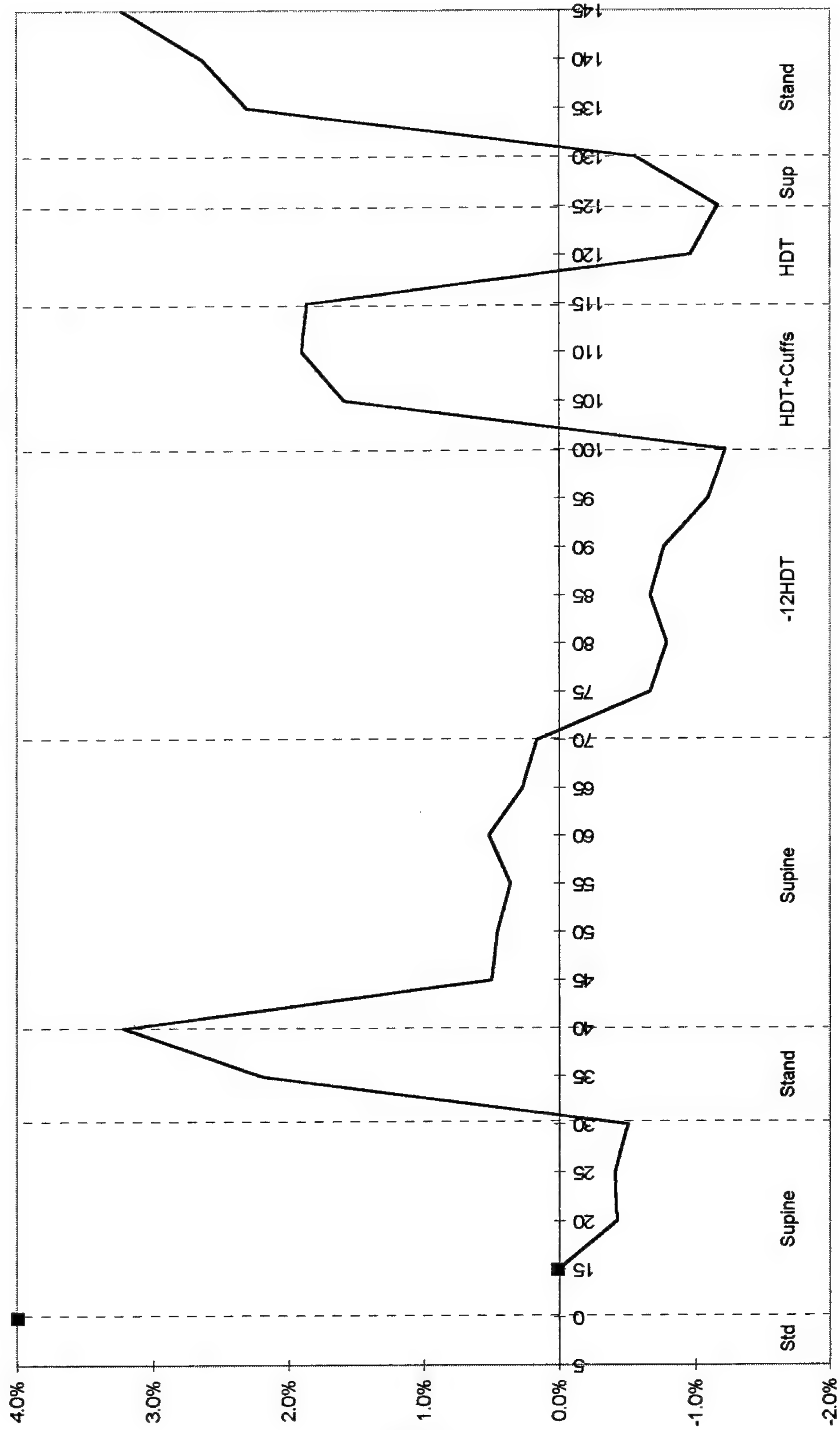


FIGURE A-10
% Leg Volume Change-Anthropometric Sleeve (Subject 10)



APPENDIX B

INDIVIDUAL ANTHROPOMETRIC AND HEMODYNAMIC MEASUREMENTS

TABLE B-1

Anthropometric Circumference and Hemodynamic Measurements (Subject 1)

Position	Time	Foot	2	3	4	5	6	7	8	Top	Heart Rate	SBP	DBP
Standing	0	207	233	286	336	328	418.5	458	496	559	94	126	90
Supine	15	203.5	231.5	284.5	330	321	419	458	494.5	559	75	108	76
	20	202	231	280.5	329	321.5	419.5	456.5	494	558	69	112	80
	25	202	231	280.5	329	321.5	419.5	456	494.5	557	69	108	80
	30	202	232	281	330	321	419	456	493.5	556.5	75	117	90
Standing	35	204	233	285.5	336	327	419	456	495	559	86	128	92
	40	205	233	285.5	337	327	420	456	496	559	86	122	88
Supine	45	202	232	281	329.5	320	417	455	493	556	69	118	84
	50	202	227.5	279	328.5	320	416.5	455	493	556.5	76	120	82
	55	202	227	277	327.5	320	417	456	494	556	62	118	90
	60	202	227.5	277	327	320	416.5	456.5	494	556	64	120	80
	65	202	228.5	277.5	327	319	417.5	455.5	494	556.5	71	120	88
	70	202	228	277	328	319	417	456	494	555.5	69	116	84
HDT	75	202	227	276	327	318	416	454	492	554	62	118	90
	80	201	227	277	326	316	416	454.5	492.5	554.5	67	120	90
	85	201	227	275.5	325.5	317	417	451.5	492	552	63	120	92
	90	201	227	277	325	317	416	450.5	492	552	76	124	90
	95	201	227	276	326	317	415.5	451.5	490	551	69	124	90
	100	201	227	276	326	317	416	452	491	551	69	130	90
VCuff	105	201	227	278	330	321	419	456	496.5	564	71	120	90
	110	203	227.5	281	332	324	420	456.5	500	566	69	120	88
	115	202	230.5	281	332	324	420	456.5	499	565	69	122	82
UnCuff	120	200.5	226	276	325	317	416	450.5	490	552	68	116	88
	125	200	226	276	325	317	416	451	491	551.5	65	108	80
Supine	130	200	227	277	326	317.5	416	454	493	555	71	116	78
Standing	135	204	230	282	332	322	417	457	499	559	84	120	90
	140	204.5	230	282	332	322	416	457	498	559	84	116	90
	145	204	231	283	333	322	415	454	496	557	84	128	95

TABLE B-2

Anthropometric Circumference and Hemodynamic Measurements (Subject 2)

Position	Time	Foot	2	3	4	5	6	7	8	Top	Heart Rate	SBP	DBP
Standing	0	226	255	309	367.5	380	360	408	458.5	508.5	88	98	74
Supine	15	222	252	308	366	369	354	408	453	503	61	108	68
	20	220	249.5	306	367	369	354	404	454	502	61	112	68
	25	219	250	306	366	368	352	403	451	502	61	108	64
	30	219	249	306	367	367	352	405	451	499	63	106	72
Standing	35	226	252	309	372	375	355	415	463	506	94	110	68
	40	225	253	310	373	375	354	414	462	507	96	90	76
Supine	45	220	251	308	369	369	352	404	452	501	47	112	64
	50	220	251	306	367	368	351	405	451	500	52	112	64
	55	220	250.5	307	367	368	350	404	452	502	54	106	64
	60	220	251	306	366	368	352	404	454	499	52	106	70
	65	219	249	306	366	367	351	404	454	499	53	112	70
	70	219	250	305	366	368	351	404	451	501	61	106	72
HDT	75	219	247	303	364	366	351	402	448	498	58	94	68
	80	217	245	302	363.5	365	350	401	448	497	53	102	74
	85	218	247	303	364	366	351	401.5	448	499	61	98	70
	90	218.5	246	303	364	366.5	351	401	449	498	63	110	74
	95	217	244	302	364	366	351	402	449	498	62	104	74
	100	218	246	303	364	366	350	401	450	497	56	106	70
VCuff	105	219	247	306	368	369	355	406	456	507	65	98	68
	110	219	247	305	368	370	355	406	455	506	68	98	68
	115	218	246	306	368	370	355	408	457	507	59	92	68
UnCuff	120	218	245	303	363	366	354	404	447	497	64	102	76
	125	216	245	302	362	366	352	405	447	498	67	104	68
Supine	130	215	245	304	365	367	352	404	449	500	62	108	68
Standing	135	222	252	309	370	371	352	414	460	506	93	100	79
	140	221	253	310	372	372	351	415	460	506	81	100	79

TABLE B-3

Anthropometric Circumference and Hemodynamic Measurements (Subject 3)

	Time	Foot	2	3	4	5	6	7	8	Top	Heart Rate	SBP	DBP
Standing	0	241	281	352	404.5	392.5	373	417	467.5	524	72	118	88
Supine	15	235.5	275	349	402	383	366.5	402.5	459	522	57	110	60
	20	236.5	275	346	400.5	384	365.5	402.5	460	521	56	108	70
	25	236.5	274.5	345	401	384	366.5	403	460	522	53	106	72
	30	237	275.5	348.5	401	384	366.5	403.5	461.5	521	61	104	68
Standing	35	238	276.5	348	406	391	369	420	467	522.5	81	110	85
	40	241	278	351	407	393	371	417	471	530	81	110	78
Supine	45	236	274.5	347	400	383	370	405	458	518	60	108	70
	50	236	274	347	400.5	383.5	368	407	458	517.5	62	106	68
	55	236.5	274	346.5	400	383	367.5	404	459	519	56	104	72
	60	236.5	273.5	346	400	383.5	367.5	404.5	458	519	56	102	72
	65	237	273.5	347	400	384	368	402.5	458.5	518.5	56	102	70
	70	236	273.5	346.5	399	382.5	366	403	458	519.5	58	100	70
HDT	75	236	273	342.5	396	383	366	403	455	518	54	102	74
	80	236.5	274	343	395	381	367	400	456	518	56	100	68
	85	236	274	341	395	381.5	368	399	456	517.5	53	100	68
	90	237	275	343	395.5	383	369	399	454.5	517	51	100	70
	95	236	274	344	395	383	369.5	398	454.5	517.5	48	102	68
	100	237.5	274	344	396	383	370	400	455	517	55	102	70
VCuff	105	237	274	346.5	399	386	371	407	461	522.5	52	110	68
	110	238	276	347.5	401	387.5	371.5	406	461.5	524	56	108	70
	115	238.5	276.5	347	401	387.5	372	398	462	523.5	58	102	70
UnCuff	120	236	275	345.5	396	383	370	401.5	457	516.5	52	106	76
	125	237	274	345	395	383	369	400.5	456.5	517	57	104	78
Supine	130	236.5	275.5	346.5	398.5	382.5	367.5	402.5	457.5	518	64	110	80
Standing	135	238	276.5	351	402.5	387.5	368	415.5	465.5	523.5	81	112	80
	140	240.5	277.5	352.5	405	390.5	369.5	416	466	523.5	78	112	82
	145	241.5	278.5	353	406	391.5	369.5	416.5	466	524	87	108	78

TABLE B-4

Anthropometric Circumference and Hemodynamic Measurements (Subject 4)

Position	Time	Foot	2	3	4	5	6	7	8	Top	Heart Rate	SBP	DBP
Standing	0	210	232	287	343	337	310	347.5	386	437	76	110	68
Supine	15	204	228	284.5	338.5	330	307	337	377	431	62	104	54
	20	204	228	284	339	331.5	308	336	376.5	431	57	98	50
	25	204	228.5	284	338	330.5	306	335.5	374	430.5	62	102	52
	30	203	228	284	337	330	306	337.5	374.5	429.5	60	100	50
Standing	35	208	233	290	344	336.5	310	344.5	382.5	437	83	110	68
	40	208.5	234	292	345	339	311	346	385	441	89	88	52
Supine	45	204	230	286	339	331	307	334	376	431.5	48	104	50
	50	205	229	287	339.5	330	307	336	373	429	47	108	52
	55	205	229	287	339	330.5	307	337.5	374.5	429.5	47	98	56
	60	206	230	288	340	331	307	337	375	430	59	108	58
	65	203	229	285	338	330	308	337	374	427	55	110	52
	70	202	227	285	338	330	306	337	374	427	57	102	54
HDT	75	202	226	281	338	329	305	332	371	425	56	106	44
	80	201	225	281	335.5	330	306	332	369	425	58	98	50
	85	201	225.5	281	335.5	330	306	335	368	425	53	100	58
	90	200	225	280	335	330	306	336	369	420.5	55	110	60
	95	199	224	279	334	330	306	335	369	421	55	108	52
	100	198.5	224	279	335	330	306	332	368	420	52	106	56
VCuff	105	200	225.5	283	339	334	310	340	377	433	57	108	54
	110	200	226.5	283.5	341	334	311	339	377	433	61	110	52
	115	200.5	226	283	340	334.5	311	340	377	433	58	112	54
UnCuff	120	197	223	279	335	330	307	334	369	421	61	110	52
	125	197	223	278	334	330	307	333	368	421	56	110	56
Supine	130	198	225	283	336	329	307	335	372	424	58	108	50
Standing	135	204	228	289	342	333	308	342	380	436	84	104	56
	140	203.5	228	289	343	336	308	342.5	380.5	436.5	88	96	56
	145	204	229	291	345	336	310	343	382	435	94	104	56

TABLE B-5

Anthropometric Circumference and Hemodynamic Measurements (Subject 5)

Position	Time	Foot	2	3	4	5	6	7	8	Top	Heart Rate	SBP	DBP
Standing	0	207	233	290	355	358	341.5	383	447	497	72	106	72
Supine	15	203.5	227.5	285	349	352	339	381.5	436	488	54	102	66
	20	201.5	228	286	348.5	350.5	339	379	434.5	489.5	55	96	62
	25	203	227.5	285	348	350	339	379	434	489	53	94	62
	30	202.5	227	286	348	350	339	378	434	488	59	90	66
Standing	35	205	231.5	288.5	355	354	339.5	380	439	493	76	96	70
	40	208	232	286	352	356	341	390	441	493	80	104	70
Supine	45	202	227	285	348	350	338	380	434	489	51	100	70
	50	202	228	284	350	350	338	379	434	487	57	106	66
	55	202	228.5	284.5	348	349.5	337.5	378.5	433.5	487	57	108	68
	60	202	229	284.5	348	348	337.5	378	434	488	55	106	66
	65	201	229.5	285	348.5	346	337	377	434	487	67	108	64
	70	201.5	229	284	347	345	337	378	434	487	58	106	68
HDT	75	200.5	228	281	344	344	337	376	432	487	54	112	68
	80	201	228.5	281	343.5	344	336	375	431.5	487	54	110	70
	85	202	229	280.5	343	344	337	375	430	486	53	112	70
	90	201	228	281	344	344	337	375	431	486	56	110	78
	95	201	226	280	343	343	338	375	429	486	53	108	72
	100	201	227	279	343	343	337	374	430	485.5	52	108	72
VCuff	105	203	230.5	286.5	350	350	340	382	442.5	494	55	110	72
	110	204	230	286	351	351	340.5	384	441.5	492	52	108	68
	115	204	231	287	351	351	340	384	443	493	52	108	70
UnCuff	120	202	227	279	343	344	337.5	375.5	430	480	51	110	70
	125	202	227	280	342	344	337	374	431	482	52	108	70
Supine	130	202	227	282	345	346	338	377	434	486	54	110	70
Standing	135	209	232	288	351.5	354	340	378	437	490	74	100	70
	140	208	232	285	347	354	338	379	437	491	78	98	74
	145	207	231	287	352	355.5	339	379	436	490	79	100	70

TABLE B-6

Anthropometric Circumference and Hemodynamic Measurements (Subject 6)

Position	Time	Foot	2	3	4	5	6	7	8	Top	Heart Rate	SBP	DBP
Standing	0	236	286	355	385	371	354	418	471	521	68	98	72
Supine	15	230	280	349	380	368	352	406	463	518	53	100	68
	20	231	280	347	379	367	351	405.5	461	520	49	106	68
	25	230	279	348	380	367	350	407	459	518	50	110	60
	30	230	280	348	379	366.5	351	407	461	517	49	102	62
Standing	35	234	284	354	386	371	354	414	467	522	90	104	80
	40	233	284	354	386.5	370	354	414	466	522	79	106	74
Supine	45	230	281	349	381	368	352	408	461	518	47	109	70
	50	230	281	350	380	367	352	409	460	517	50	98	70
	55	230	280	350	380	367	351	406	458	517	52	110	72
	60	230	280	349	380	367	352	408	459	516	51	104	70
	65	230	281	349	380	367	352	407	459	517	54	100	72
	70	230	280	349	379	365.5	351	406.5	460.5	515	53	112	70
HDT	75	227	277	344	377	365	351.5	403.5	456	516	59	106	66
	80	228	277	344	377	366	351.5	403	454.5	516	55	98	68
	85	227	276	343	376	365	350	403	455	513	53	106	72
	90	227	276	343	375	365	347	402	454	512	54	104	68
	95	227	276	343	375	364.5	350	403	455	513	53	110	72
	100	227	276	341.5	374.5	364	350.5	401	455	514	50	104	68
VCuff	105	229	280	346	377	367	351.5	406	458	521	53	106	68
	110	229	280	346	379	368	352	408	460	522	57	110	70
	115	229	278	346	379	368	353	407	461	523	54	110	70
UnCuff	120	226.5	275	341.5	374	365	351	401	456	508	52	114	70
	125	227	275	342	375	365	350	404	456.5	510	56	110	70
Supine	130	227	278	344	375	365	350	402	456	508	52	112	70
Standing	135	230	281	349	379	366	352	412	461	515	81	120	80
	140	231	282	350	380	367	354	412	461	513	98	106	72
	145	232	281	350	380	367	355	413	461	514	86	106	70

TABLE B-7

Anthropometric Circumference and Hemodynamic Measurements (Subject 7)

Position	Time	Foot	2	3	4	5	6	7	8	Top	Heart Rate	SBP	DBP
Standing	0	239.5	297	367	399	377	357	444	490	537	80	118	92
Supine	15	236	293	363	397	377	358	436	487	531	47	132	68
	20	235.5	292	362	397	377	359	437.5	486	529	53	122	70
	25	236	292	362.5	397	377	358	437	486	529	48	120	62
	30	236	293	361	397	377	357	434	485.5	529.5	48	128	62
Standing	35	237	294	364	401	381.5	358	445	490	534	84	118	90
	40	237.5	293.5	365	401	383	358	446	491.5	534.5	80	120	90
Supine	45	236	292	362	396	377	359	438	485	524.5	56	116	62
	50	235.5	292	362	397	377	358	438.5	486	525	50	124	70
	55	235	292	363	396.5	377	357	438	486	524	48	124	62
	60	236	292	363	396	377	355	437	484.5	524	48	118	68
	65	235.5	291	361	396	375.5	356	437	485	525	54	124	68
	70	234	292	361	396	376	354.5	437	484.5	525	48	118	70
HDT	75	233.5	290	360	394	375	356	433	483	524	56	116	70
	80	234	291	359	392	374	354	432	483	523	49	120	70
	85	233	289	359	392.5	375	354	432.5	484	524	49	116	70
	90	233	289.5	358	393	375	355	432	482	523	51	116	70
	95	233	289	358	393.5	376	352.5	433	482.5	522.5	49	116	70
	100	233	289	357.5	392	375.5	353	431.5	482	522.5	50	128	70
VCuff	105	233	290	361.5	397	379	357	438	488	529.5	48	126	80
	110	234	291	361.5	398	381	358.5	440	491	530.5	53	112	76
	115	235	291	363	397.5	380	358	440	490	530	48	128	72
UnCuff	120	232	289	359	394	376	352.5	433	483	522	50	128	68
	125	231	289	359.5	393.5	376	354	432.5	482	523	57	130	66
Supine	130	233.5	290.5	360	394	376	354	437.5	485	526	58	126	66
Standing	135	237	292	360	397.5	378	356	442	490	532	68	118	78
	140	236	291	364	399	381	357	443.5	491.5	532	78	120	84
	145	236.5	292	365	400	380	357	446	494	534	76	122	90

TABLE B-8

Anthropometric Circumference and Hemodynamic Measurements (Subject 8)

Position	Time	Foot	2	3	4	5	6	7	8	Top	Heart Rate	SBP	DBP
Standing	0	218	239	283.5	343	354	335	400	443	499	72	130	88
Supine	15	218	241	285	341	351	334	391	443	496	56	104	68
	20	212	237	281.5	339	350	331	388	439	496	56	116	78
	25	210.5	237	282	339	350	330	386	438	496	59	118	70
	30	212	238	284	341	352	330	387	438	496	57	116	76
Standing	35	215	241	286	346	358	337	405	444	503	104	124	95
	40	218	242	286	347	359	339	403	445.5	501	83	130	96
Supine	45	212	237	283	340	351	330	394	439	494	53	108	80
	50	211	239	284	341	350	331	395	440	493	53	104	68
	55	210	237	284	340	348	330	395	436	494	54	118	74
	60	211	236	282	340	347	330	394	434	490	59	116	72
	65	211	236	282	340	348	330	393	432	489	54	118	70
	70	211	235	281	338	346	327.5	390	433	490	60	120	77
HDT	75	210	234	278	334	344	326	385	430	484	52	116	78
	80	210	234	279	334	343	326	382	428	485	51	120	74
	85	210	232	277	334	343	326	381	425	486	59	116	87
	90	210	232.5	276	333	342.5	326	380	426	485	63	120	70
	95	209	232	276	331	342	324	380	426	484	60	120	78
	100	208	231	276	331	341	323	380	425	484	57	110	78
VCuff	105	210	236	281	337	346	327	386	433	494	59	128	72
	110	210	235	282	336	346	329	387	435	494	57	112	60
	115	210	235	281	336	346	327	385	435	494	62	118	70
UnCuff	120	208	232	276	331	340	324	378	424	486	56	118	80
	125	208	231	276	331	340	324	379	424	485	58	120	78
Supine	130	211	233	280	334	341.5	325	384	426	486	60	120	78
Standing	135	212	238	282	340	349	328	392	435	494	93	126	98
	140	214	240	281	340	350	330	396	435	492	84	128	98

TABLE B-9

Anthropometric Circumference and Hemodynamic Measurements (Subject 9)

Position	Time	Foot	2	3	4	5	6	7	8	Top	Heart Rate	SBP	DBP
Standing	0	220	264	330	384	377	354	437.5	509	561	84	118	72
Supine	15	218	260	328	378	373.5	353	432	502	561	63	112	80
	20	217.5	261	328	379	373	353	433	501	558	68	120	76
	25	217	260	328	379	373	353	433	502	557	61	106	74
	30	217	261	329	379	373	353	432	501	556	59	110	80
Standing	35	220	264	332	385	377	354	436	507	564	78	98	78
	40	220	265	333	386	377	355	437	507	564	90	118	80
Supine	45	216	261	328	379	372	352	436	501	559	64	120	68
	50	216	261	329	378	372	353	432	502	556	68	128	78
	55	216	260	329	379	371	352	433	503	556	63	128	67
	60	216	260	329	379	372	352	433	503	557	60	114	72
	65	216	261	329	378	372	351	433.5	505	557	63	130	82
	70	216	261	328	378.5	372	351	432	502	557	62	114	78
HDT	75	215	259	326	377	370	353	431	500	556	60	122	72
	80	216	258	324	377	369	352	431.5	500	556	58	114	74
	85	215.5	258	325	376	369	353	431	500	555	60	116	72
	90	216	258	325	376	369	352	430.5	499	556	56	116	80
	95	215	258	324	376	369	352	430	499	556	54	120	70
	100	216	258	324	376	369	353	429	499	556	56	106	74
VCuff	105	216	261	328	380	372	354	434	504	563	58	114	76
	110	217	261	328	380	372	355	433	505	562	57	104	74
	115	217	261.5	328	381	372	355	435	505	563	58	120	62
UnCuff	120	216	260	325	377	369	353	430	500	555	59	114	72
	125	216	260	326	376	369	354	429	500	555	59	116	68
Supine	130	216	261	326.5	378	370	353	430	502	556	63	120	80
Standing	135	219	264	329	382	373	355	436	507	561	78	124	76
	140	220	264	330.5	385	376	356	438	508	564	81	122	74

TABLE B-10

Anthropometric Circumference and Hemodynamic Measurements (Subject 10)

Position	Time	Foot	2	3	4	5	6	7	8	Top	Heart Rate	SBP	DBP
Standing	0	209	245	296	351	339.5	327	371	414	462	68	120	80
Supine	15	203	240.5	291	346	333	324	360	405	453.5	49	110	70
	20	203	239	292	343	333	325	358.5	404	452	53	108	72
	25	203	239	290	345	333	324	359	405	451	52	108	66
	30	203	240	291	344	333.5	324.5	358	403	452	50	120	70
Standing	35	207	243	297	350	339	324	363	410	458	73	120	84
	40	211	245	296	352	341	325	366	412	459	74	126	88
Supine	45	204.5	242	294	346	334	324.5	362	404.5	452	48	118	68
	50	204	241	293	347	333	324	361.5	405.5	454	50	104	70
	55	204	241	292	345	332	325	361	406.5	455	49	112	68
	60	204.5	241.5	293	346.5	332	325	361	406	455	50	104	66
	65	204.5	241	294	346	332.5	323.5	360	406	454	50	110	68
	70	204	241	294	345	332	324.5	360	405	454	51	112	66
HDT	75	203	240	290	343	331	324.5	359	404	451	47	112	80
	80	202	239.5	289.5	342	331	325	359	404	450.5	63	116	70
	85	202	239	290	343	331	325	359.5	404	450.5	50	116	70
	90	202	239	290	343	331	325	358.5	404	450.5	63	108	72
	95	202	239	289	342	331	324.5	358	403	450	49	112	62
	100	202	238.5	288.5	342	331	325	357	402.5	450.5	53	110	72
VCuff	105	203	240.5	291	345	335	327	363.5	411	462	60	110	68
	110	203.5	241	291.5	345	336	327	364	412	463	57	114	76
	115	204	240	292	345	336	327	365	411	462	50	118	72
UnCuff	120	203	238	288.5	341	331.5	325	358.5	404.5	450	52	118	80
	125	203	238	288	341.5	331	325	358.5	403	449	49	118	78
Supine	130	203	239	290	342.5	332	325	358.5	405	452	51	122	84
Standing	135	208.5	243	294	346	335	326	368	411	459	63	108	82
	140	208.5	243	295	347.5	336	326	369	411	459	72	118	80
	145	210	243	295	348	337.5	326	371	413	460	70	114	80

APPENDIX C

INDIVIDUAL FILTERED STRAIN GAUGE DATA FIGURES

FIGURE C-1
% Leg Volume Change - Filtered Strain Gauge Data (Subject 1)

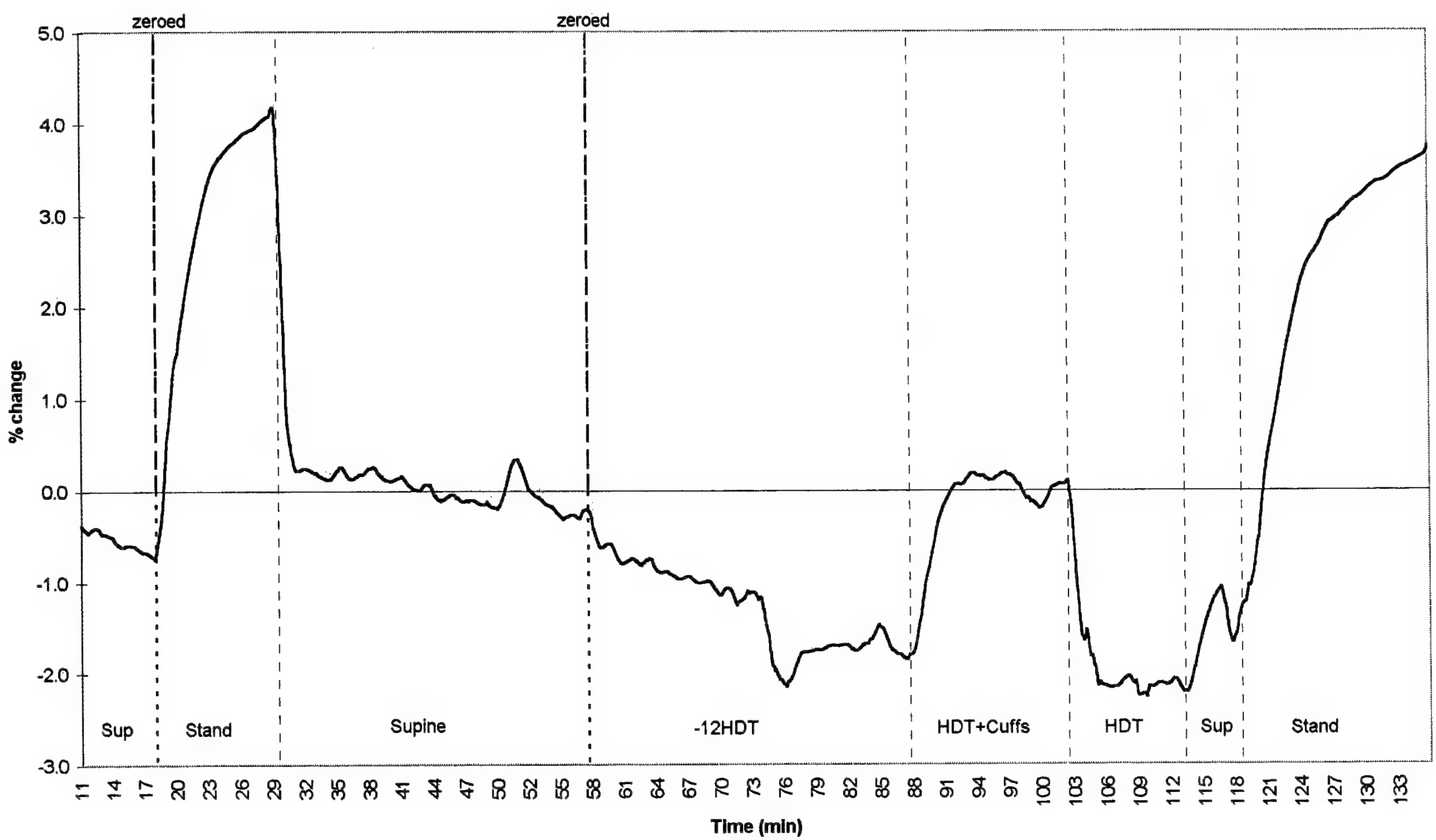


FIGURE C-2
% Leg Volume Change-Filtered Strain Gauge Data (Subject 2)

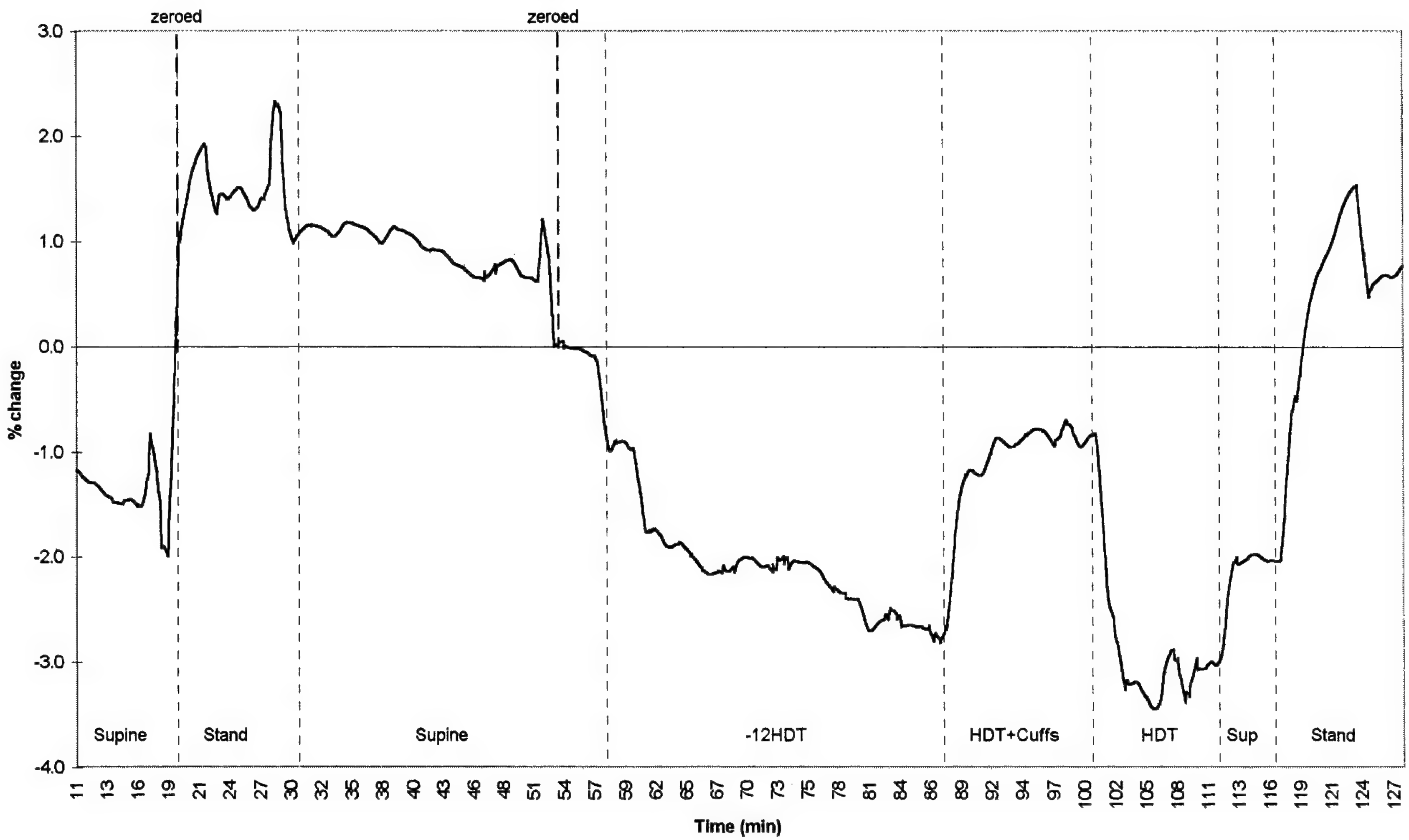


FIGURE C-3
% Leg Volume Change-Filtered Strain Gauge Data (Subject 3)

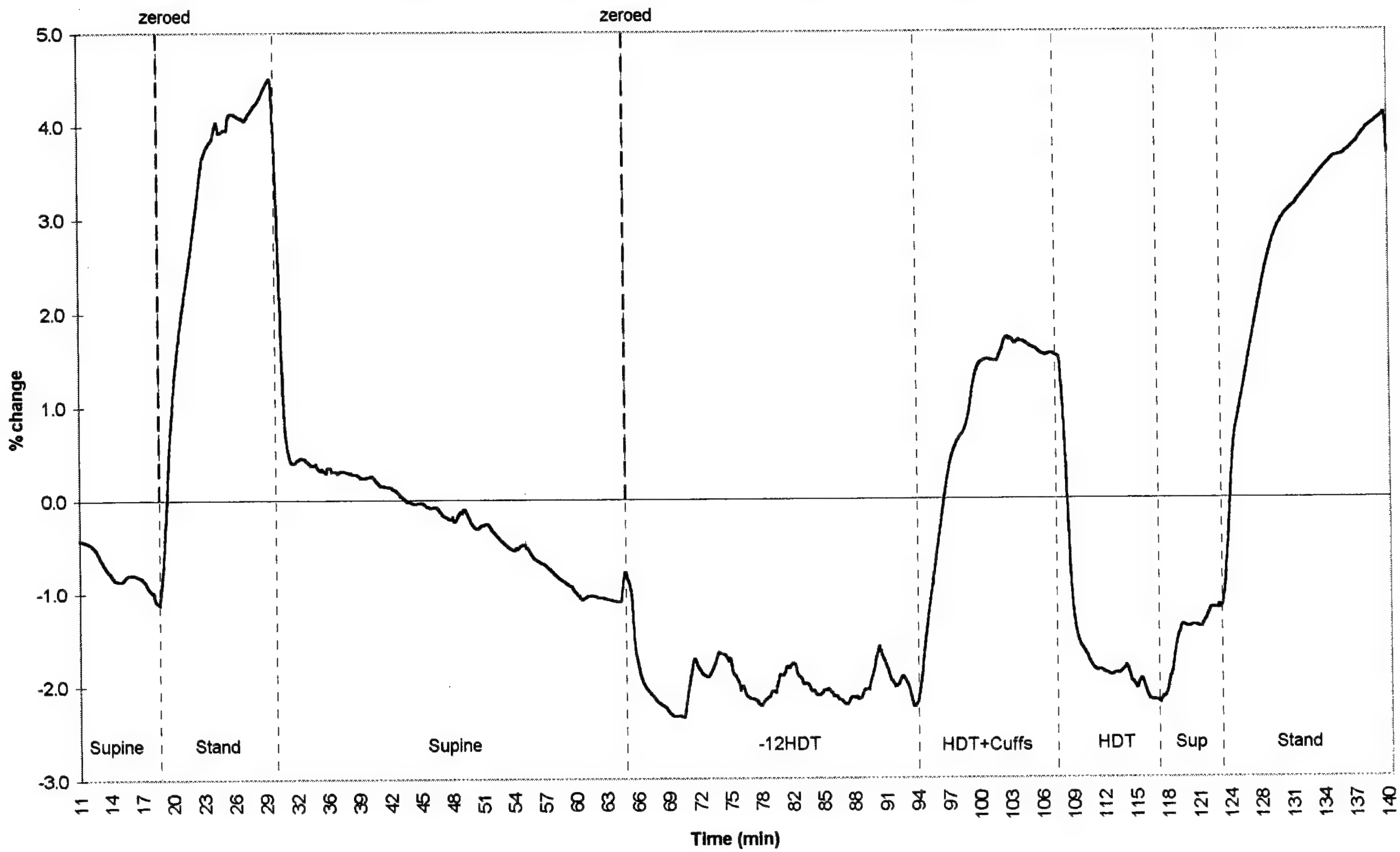


FIGURE C-4
% Leg Volume Change-Filtered Strain Gauge Data (Subject 4)

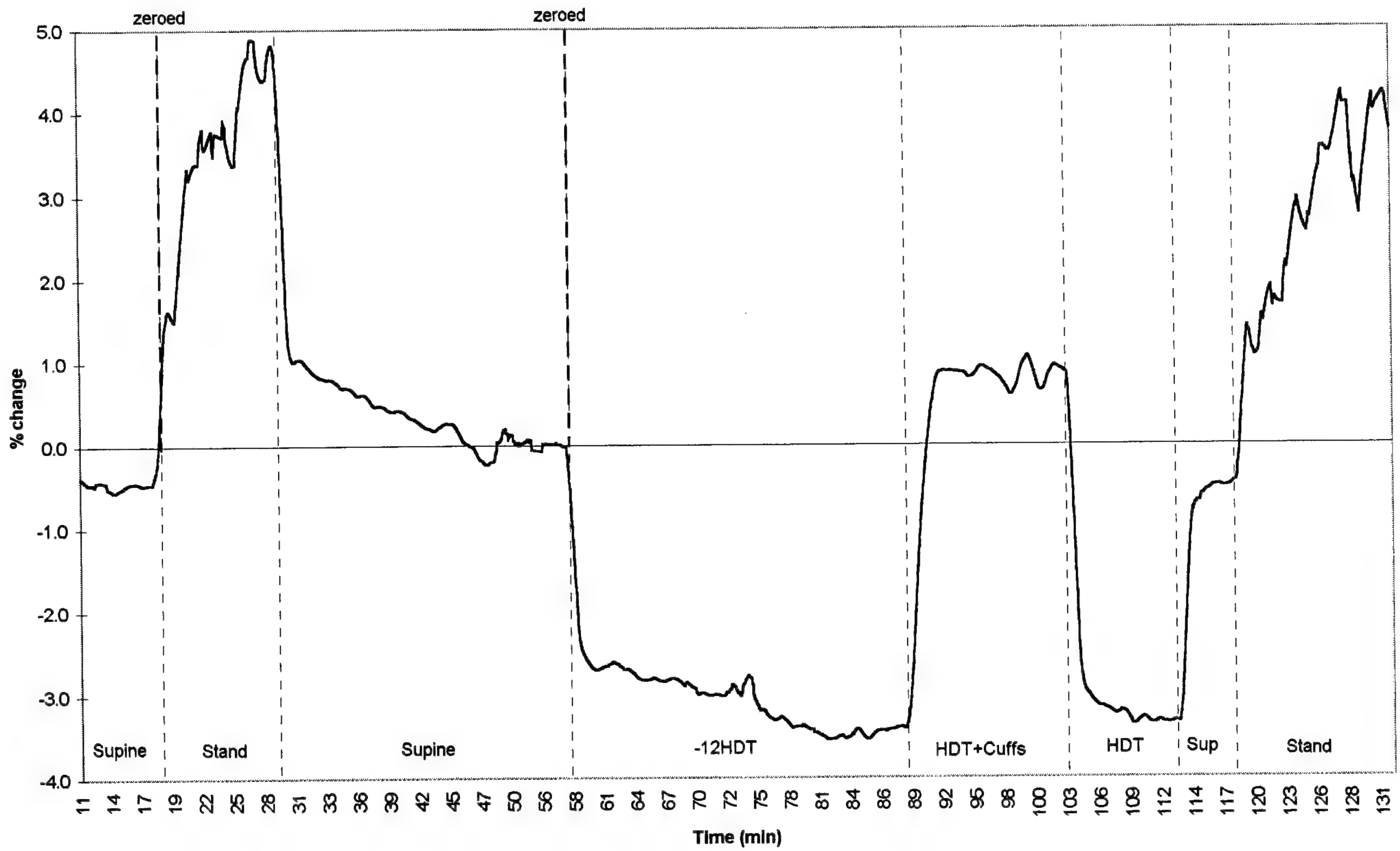


FIGURE C-5
% Leg Volume Change-Filtered Strain Gauge Data (Subject 5)

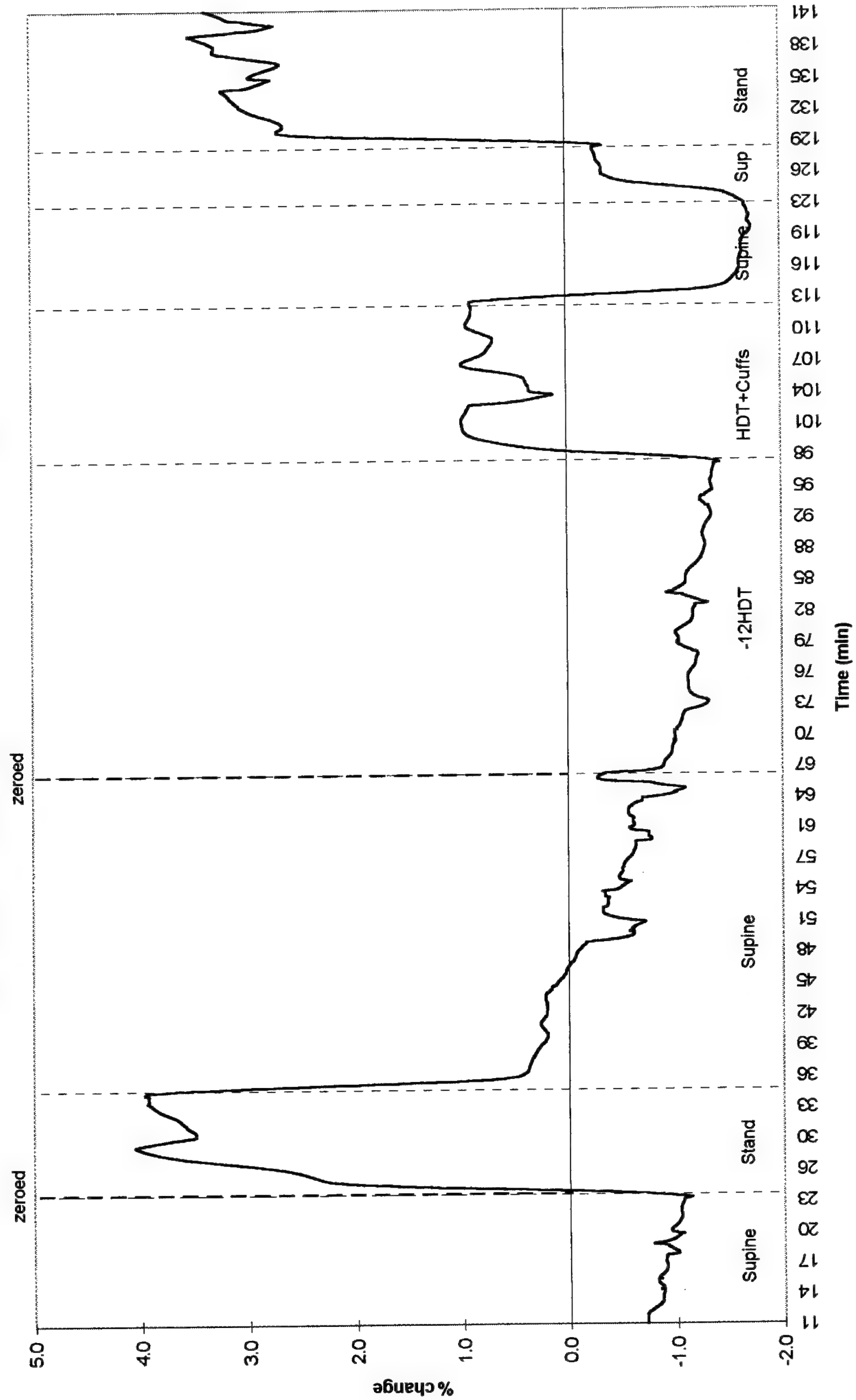


FIGURE C-6
% Leg Volume Change-Filtered Strain Gauge Data (Subject 6)

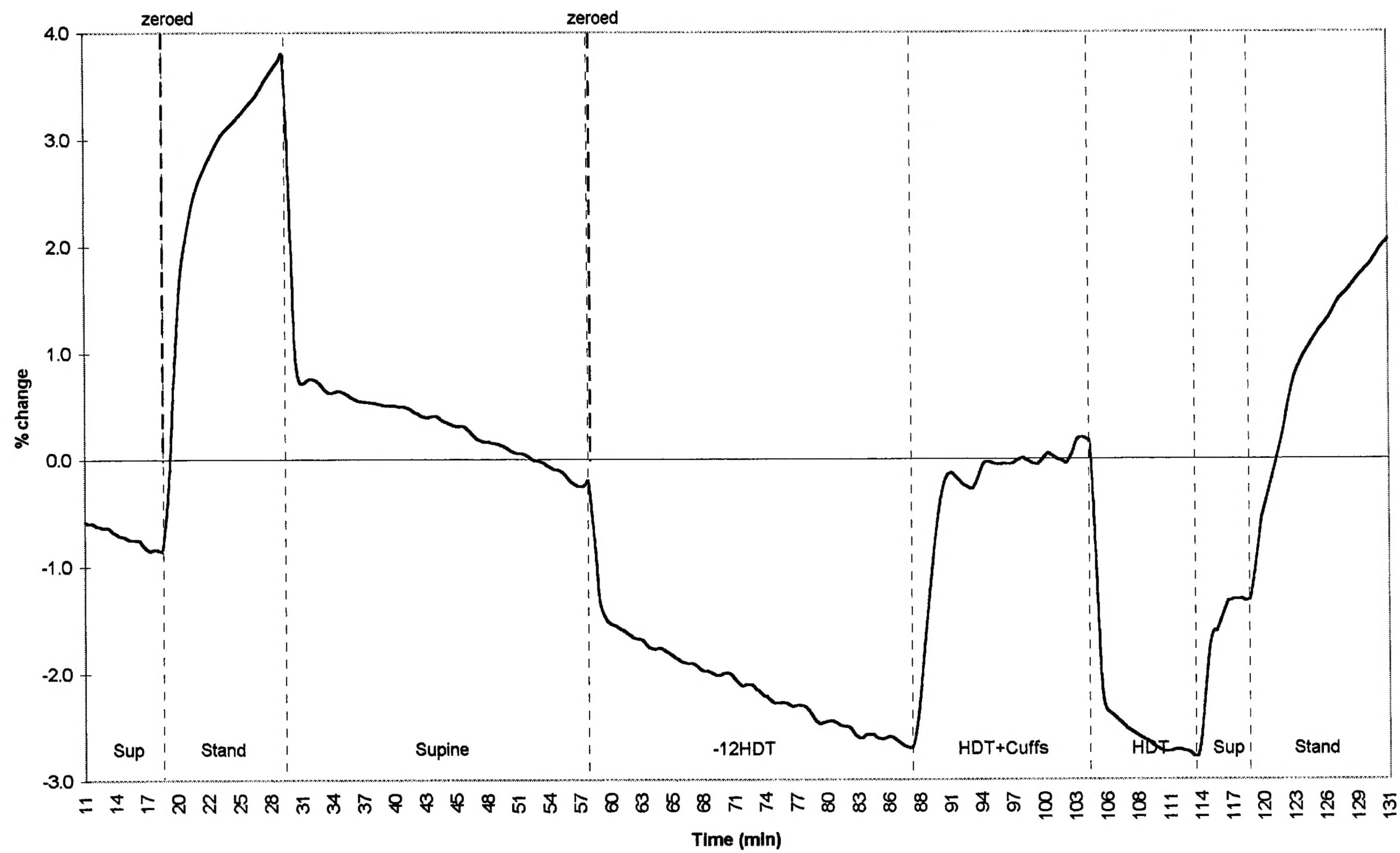


FIGURE C-7
% Leg Volume Change-Filtered Strain Gauge Data (Subject 7)

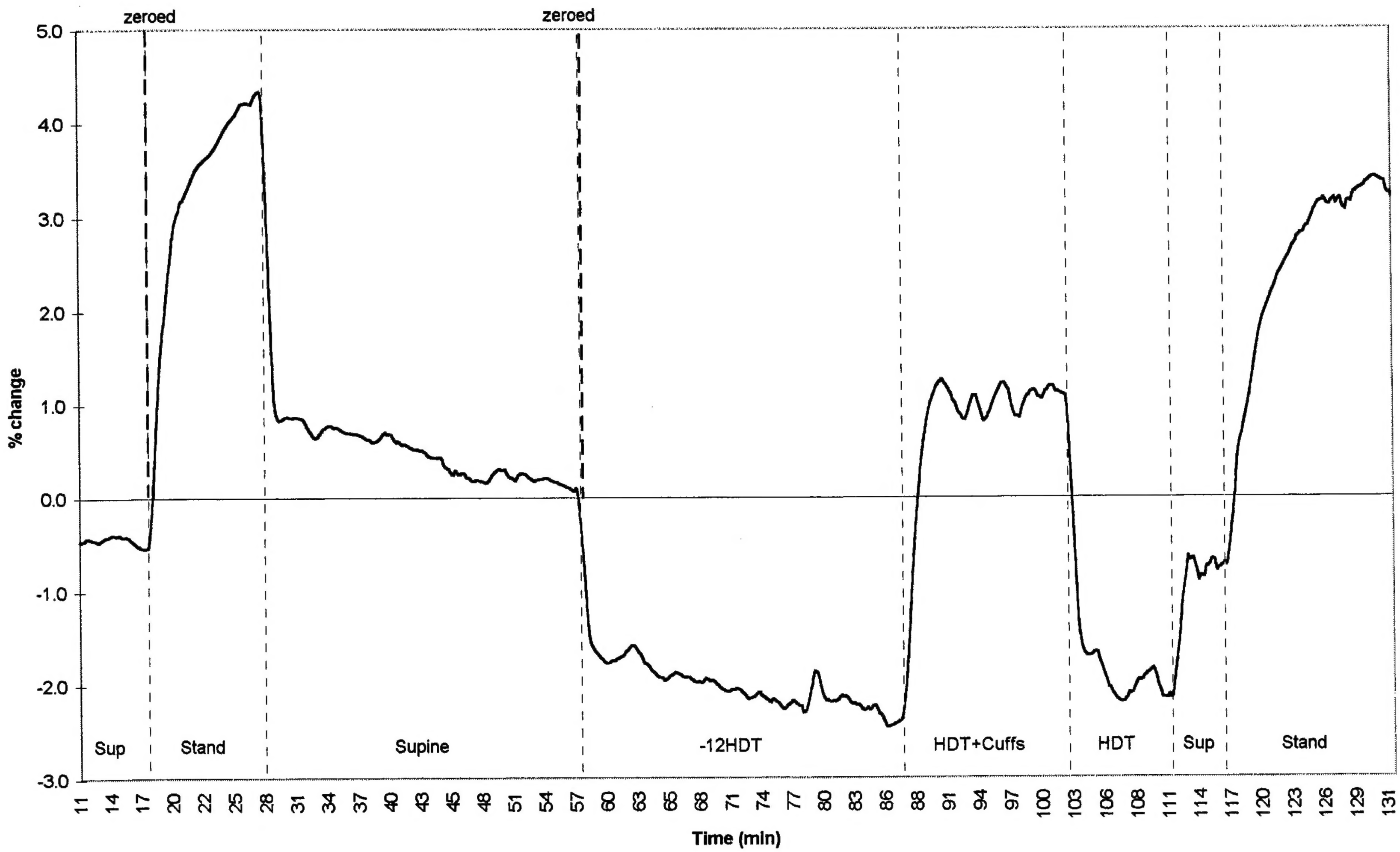


FIGURE C-8
% Leg Volume Change-Filtered Strain Gauge Data (Subject 8)

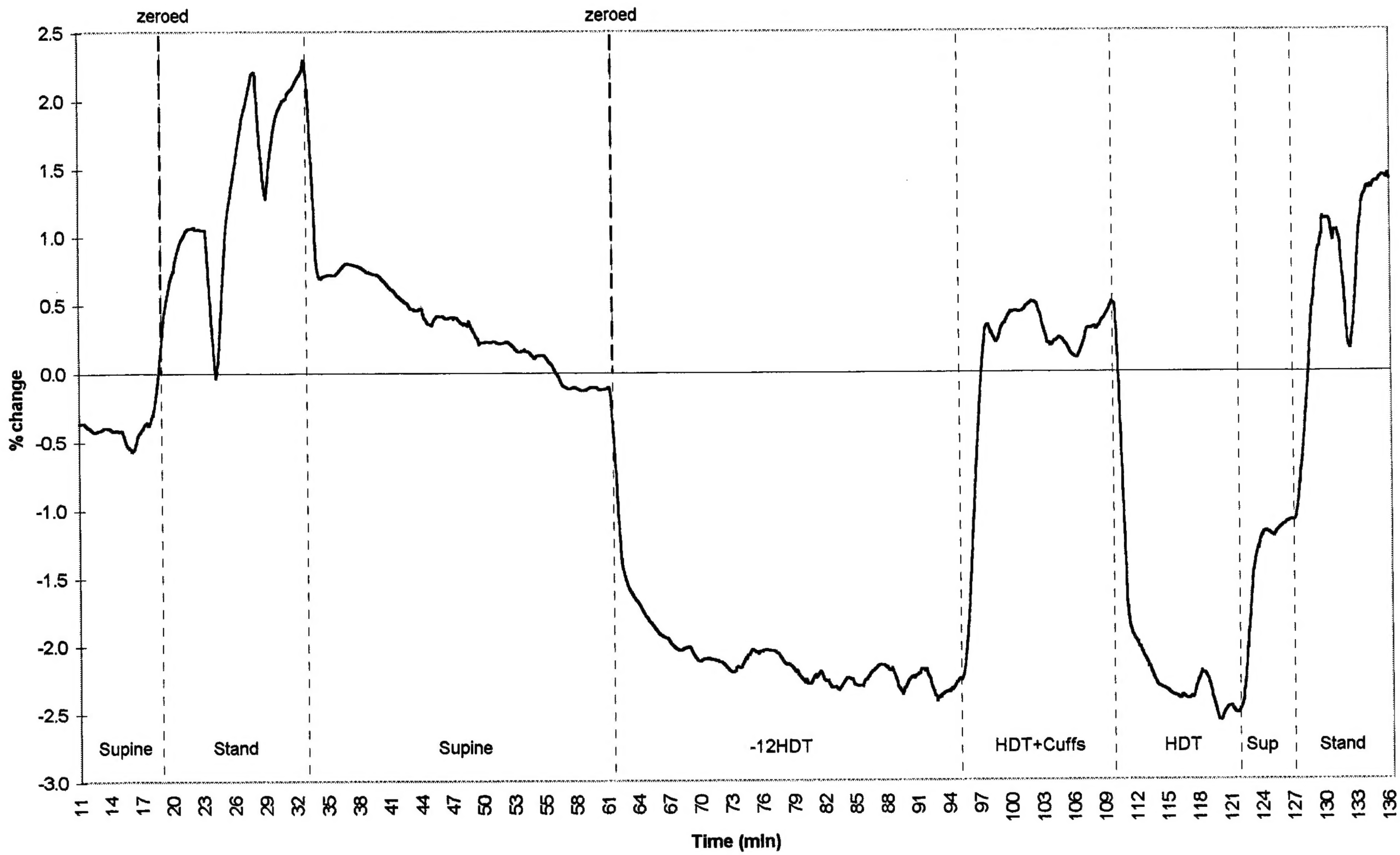


FIGURE C-9
% Leg Volume Change-Filtered Strain Gauge Data (Subject 9)